BIOLOGIC AGENTS

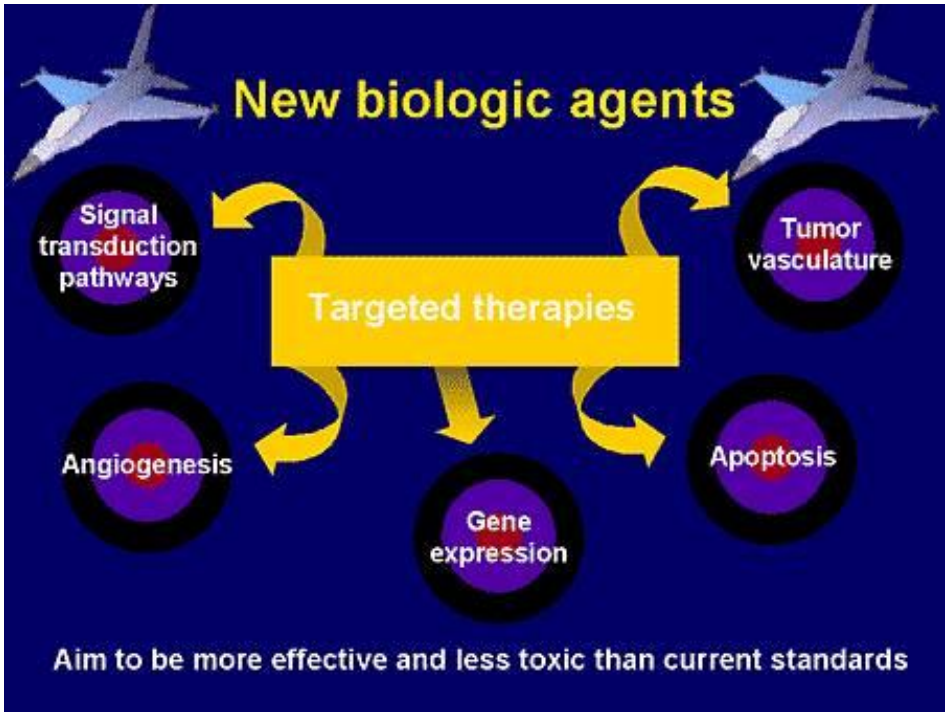
BY Dr /Aliaa Omar El-hady

BIOLOGIC AGENTS (1)

==========

سنبدأ ان شاء الله فى هذه الجزئية الهامة جدا من الغد ان شاء الله تابعونا

See Translation



BIOLOGIC AGENTS (2)
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Biologic agents are currently available for use in the treatment of inflammatory rheumatic diseases:
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With our increasing understanding of the pathogenesis of autoimmune rheumatic diseases, several biologic agents have been developed for treatment, especially for RA, AS,PsA, and SLE.

These can be classified as follows:
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4 مجموعات (cytokine- B-cell- T-cell- complement)

1- Cytokine-targeted therapies.
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a- Tumor necrosis factor (TNF)-α inhibitors:
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etanercept,
infliximab,
adalimumab,
golimumab,
certolizumab.

b- Interleukin (IL)-1 inhibitors:
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anakinra,
rilonacept,
canakinumab.

c- Anti-IL-6 receptor:
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tocilizumab.

d- Anti-IL-12/IL-23:
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ustekinumab.

f- Oral tyrosine kinase inhibitors:
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tofacitinib (Janus activated kinase [JAK] inhibitor).

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2- B cell targeted therapies.
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a- Rituximab (anti-CD20).

b- B cell growth factor inhibitors:

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belimumab (anti-Blys).

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3- T cell targeted therapies.
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Costimulatory molecule inhibitors:

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abatacept (anti-CD80/86).

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4- Complement targeted therapies.
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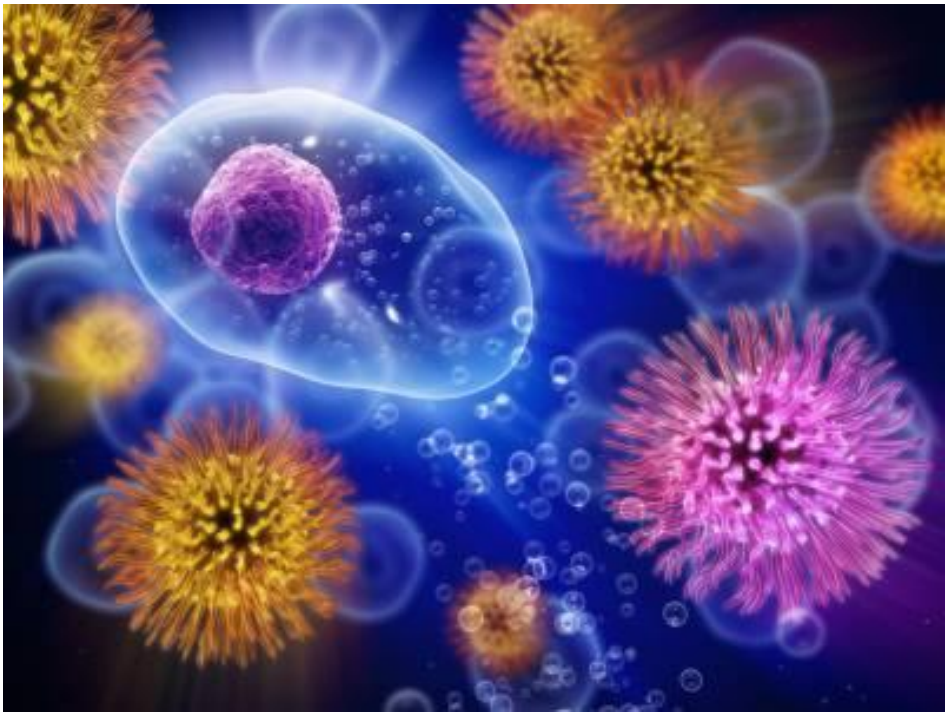
Eculizumab (anti-C5a/C5b-9).



BIOLOGIC AGENTS (3)

==========

يا ترى بيتسموا على اى اساس ..... لهم بروتوكول معروف لنهايات كل اسم دلالة ....تعالوا نعرفه بحيث ان اول ما تشوف المركب تعرف بيشتغل ازاى

What nomenclature is used in naming the biologic agents?

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• -cept:

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receptor drug which prevents a ligand from binding to its receptor (e.g., etanercept, abatacept, rilonacept).

• -ximab:

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chimeric monoclonal antibody (e.g., infliximab, rituximab).

• -zumab:

---

humanized monoclonal antibody (e.g., certilizumab, tocilizumab, eculizumab).

• -mumab:

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fully human monoclonal antibody (e.g., adalimumab, golimumab, belimumab, ustekinumab).

• -ra:

---

receptor antagonist (e.g., anakinra).

• -tinib:

---

inhibitor (e.g., tofacitinib).

BIOLOGIC AGENTS (4)
==========
خلى بالك قبل ما تدى اى علاج بيولوجى لازم تعمل شوية احتياطات
List the precautions that should be done before starting any biologic agents.
==========
=
1- Establish and record disease activity.

2- Screen for comorbidities:
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infection risk,
HIV risk factors,
hepatitis B/C risk factors,
history of malignancy (lymphoma, melanoma, others),
history of demyelinating disease,
history of tuberculosis (TB),
history of fungal exposure,
hyperlipidemia,
liver disease,
pregnancy,
medications.

3- Vaccination status:
---
patients should receive inactivated influenza vaccine (seasonal) and age-appropriate pneumococcal, meningococcal, and Haemophilus influenzae B (Hib).

Give herpes zoster vaccine (live) at least 2 to 4 weeks before biologic use.

4- Tests before use:
---
complete blood count (CBC),
creatinine,
hepatic enzymes,
lipids,
C-reactive protein,

hepatitis B and hepatitis C serologies,
purified protein derivative (PPD) (or interferon gamma release assay),
chest X-ray,
HIV (if risk factors).

BIOLOGIC AGENTS - Cytokine-targeted therapies(5)

The rationale behind the use of the biologics to inhibit cytokines in inflammatory diseases such as RA

TNF-α, IL-1, and IL-6 are key cytokines in the pathophysiology of inflammatory synovitis and destruction of bone and cartilage.

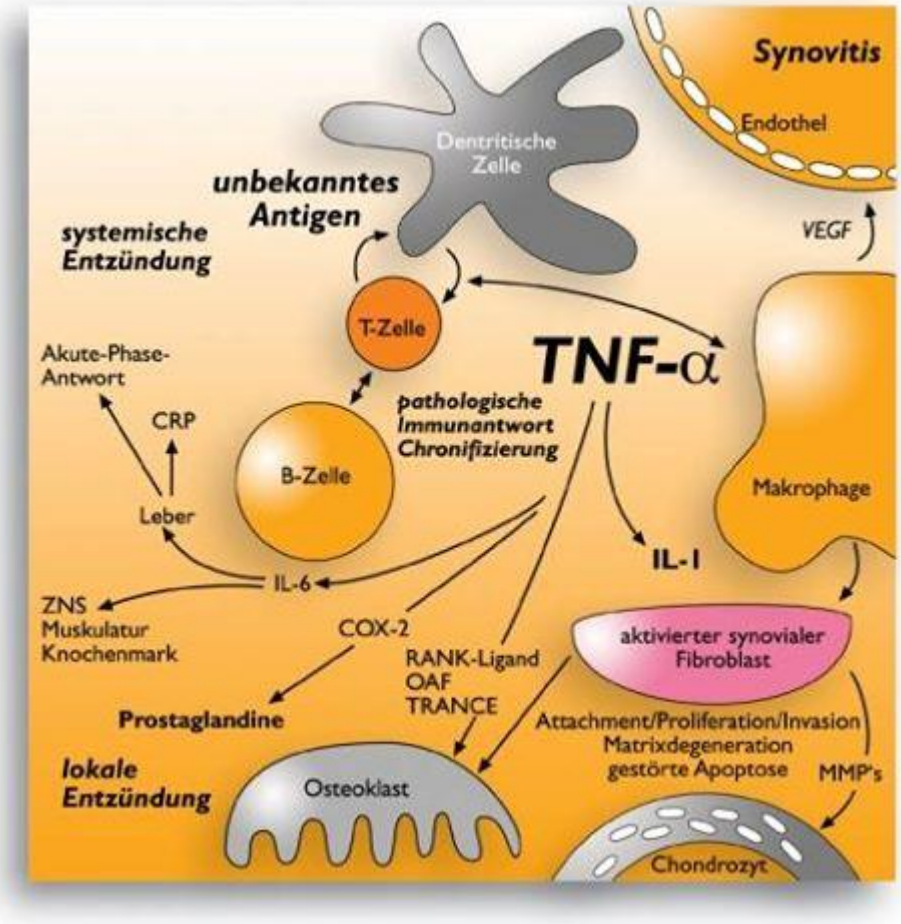
1- TNF-α

-Is initially expressed as a transmembrane molecule on the surface of macrophages.

-The extracellular portion is cleaved by TNF-α converting enzyme (TACE) to form a soluble molecule that circulates as a homotrimer.

-TNF-α (and TNF-β from T cells) binds to two receptors, TNF-RI (p55) and TNF-RII (p75), both of which are found on the surface of most cells.

-Binding of TNF-α to its receptor triggers a variety of intracellular signaling events, inducing production of prostaglandins and proinflammatory cytokines, endothelial cell expression of adhesion molecules that help recruit neutrophils and monocytes into the
synovial fluid, and synoviocyte/chondrocyte production of matrix metalloproteinases (collagenase), which can destroy cartilage and bone.


Synovitis
Endothel
Dentritische Zelle
unbekanntes Antigen
systemische Entzündung
VEGF
T-Zelle
TNF-α
Akute-Phase-Antwort
CRP
pathologische Immunantwort Chronifizierung
B-Zelle
Makrophage
Leber
IL-1
IL-6
ZNS
Muskulatur
Knochenmark
COX-2
RANK-Ligand
OAF
TRANCE
aktivierter synovialer Fibroblast
Prostaglandine
Attachment/Proliferation/Invasion
Matrixdegeneration
gestörte Apoptose
MMP's
lokale Entzündung
Osteoklast
Chondrozyt

BIOLOGIC AGENTS - Cytokine-targeted therapies(6)
==========

2- IL-1
=======

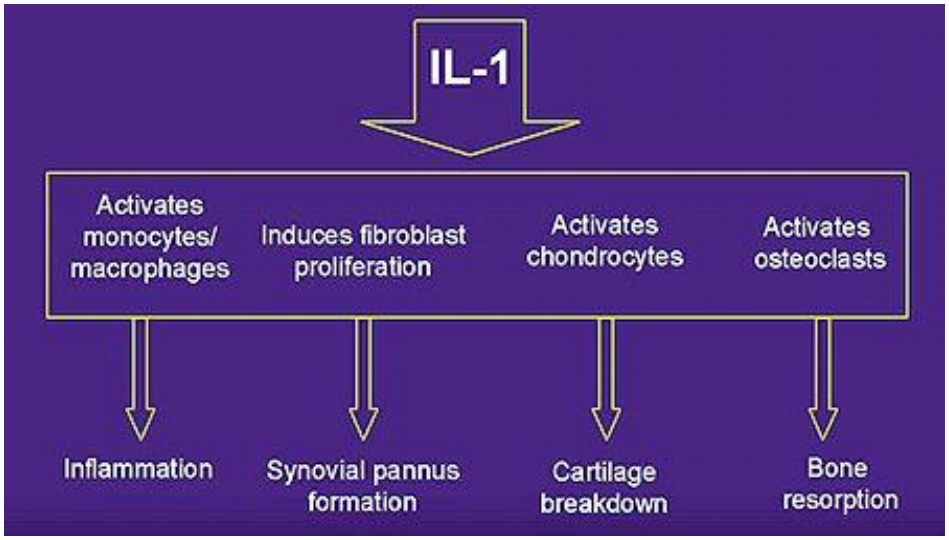
-Is a proinflammatory cytokine which exists in two forms, IL-1α and IL-1β, which are transcribed from closely related but distinct genes.

-IL-1α is in the cytosol and is membrane bound.

- IL-1β is secreted into the extracellular space after cleavage of pro-IL-1β by IL-1β converting enzyme (ICE, caspase 1).

-Thus, IL-1β is the predominant form that binds to the IL-1 receptor triggering intracellular signaling leading to a proinflammatory
response, (which is synergistic to that induced byTNF-α), B cell activation and rheumatoid factor production, cartilage degradation by induction of synoviocyte/chondrocyte production of enzymes resulting in proteoglycan loss, and stimulation of osteoclasts causing bone resorption.

-Notably, cells producing IL-1 also produce IL-1Ra. However, in patients with inflammatory synovitis such as RA, the amount of IL-1Ra in the synovium is produced in insufficient amounts to neutralize the amount of locally produced IL-1.



BIOLOGIC AGENTS - Cytokine-targeted therapies(7)
==========

3- IL-6
======

-Is critical for inflammatory and immune responses.

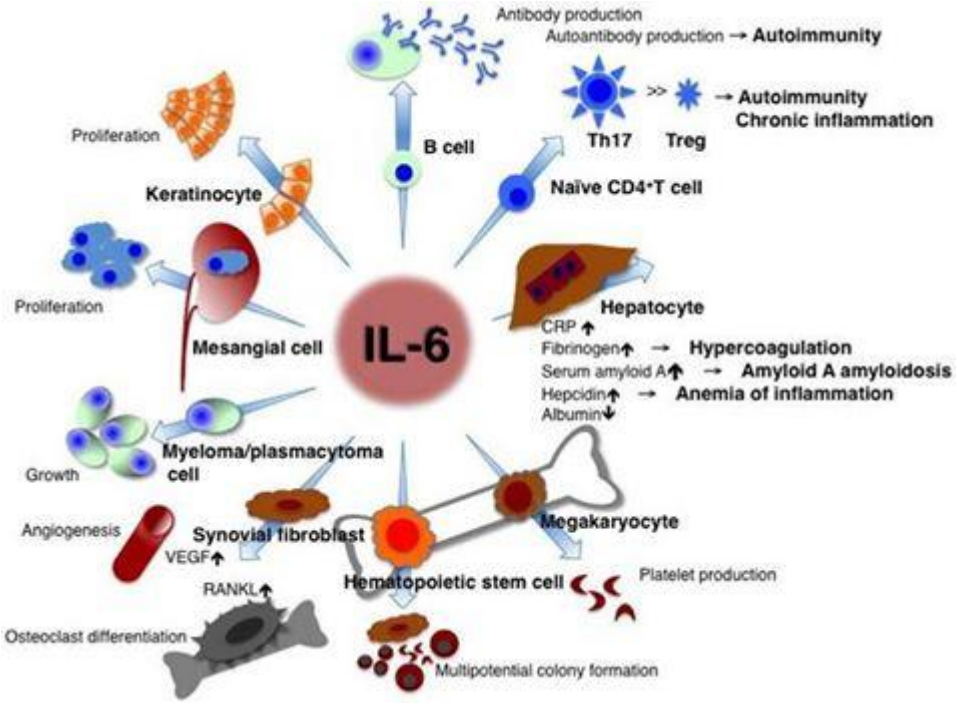
-It binds to its receptor, IL-6R, which is constitutively associated with glycoprotein 130 (gp130) on the cell membranes of hepatocytes and some leukocytes.

-Notably, binding of IL-6 to this cell membrane bound IL-6R on hepatocytes and leukocytes has an antiapoptotic/antiinflammatory effect.

-Additionally, there is a soluble form of IL-6R which can bind IL-6 and this complex can interact with gp130 on a wide variety of cells that are usually not affected by IL-6.

-This soluble IL-6/IL-6R complex is proinflammatory.

-IL-6 stimulates the development of T helper 17 (Th17) cells which produces IL-17, has a role in the activation of B cells and osteoclasts, helps recruit neutrophils, and acts synergistically with other cytokines to cause pannus formation.



BIOLOGIC AGENTS - anti- TNF-α(8)
==========
ايه هم العلاجات البيولوجية اللى بتشتغل بتثبط عمل ال TNF
Biologic agents are currently available to inhibit TNF-α

علاجات .... تعالوا نتابعها واحد واحد 5
1- Etanercept (Enbrel):
==========
-A bioengineered molecule derived from Chinese hamster فأر ovary cells which consist of a fusion protein created by linking the extracellular binding regions from two TNF-RII (p75) receptors to
the Fc portion of human immunoglobulin G1 (IgG1).

-This molecule is a dimeric soluble TNF receptor that binds soluble TNF-α and lymphotoxin (TNF-β).

-Its half-life is 3 to 5 days.

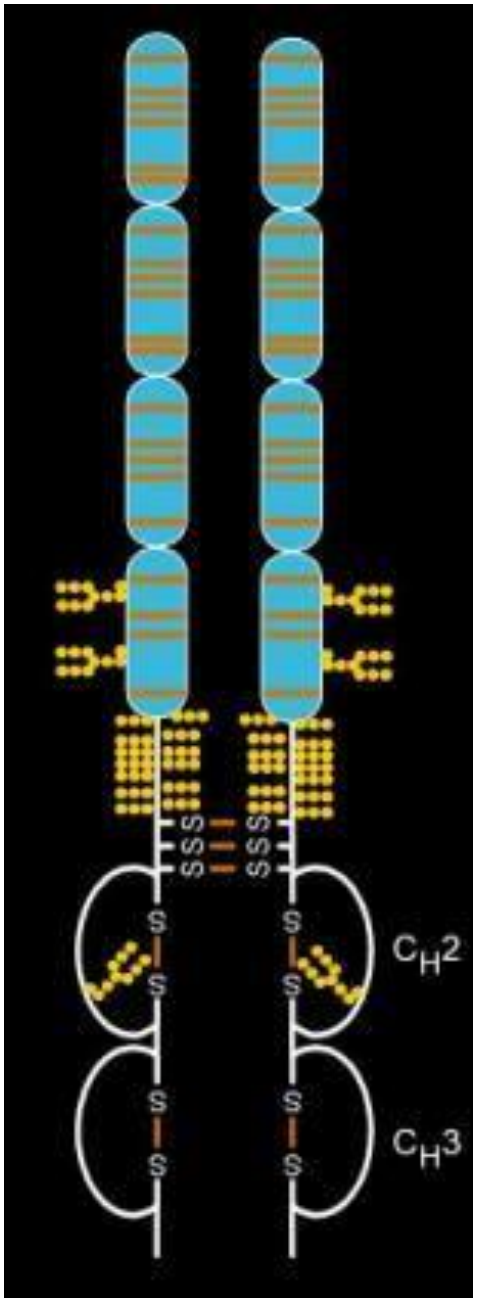
• Available formulations:
single use 25-mg and 50-mg prefilled syringes; single use 50-mg SureClick autoinjector; single use vial with 25 mg of lyophilized powder for reconstitution.
فيه منه الحقن المتعبية جاهزة وفيه منه الفايل البودر اللى بتحضرة .... فى الكومنت الاول فيديو بسيط ازاى تعلم المريض يحضر الحقنة وازاى يحقنها لنفسه

• Dosage:
RA, PsA, AS: 25 mg subcutaneously (SC) twice a week or 50 mg SC once a week.

• Skin psoriasis:
50 mg SC twice a week for first 12 weeks then once a week.

• In RA, typically used in conjunction with MTX or another synthetic disease-modifying antirheumatic drug (DMARD).

-Not effective for uveitis in spondyloarthropathies. هاااااااااام
Should not be used if an patient with AS has uveitis or inflammatory bowel disease.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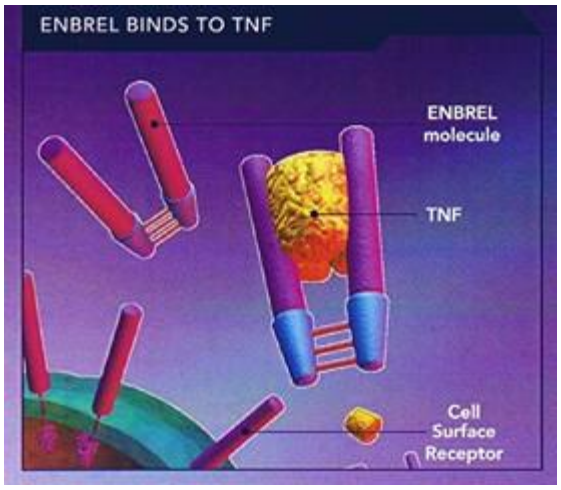
C_H3


ENBREL BINDS TO TNF
ENBREL molecule
TNF
Cell Surface Receptor


50 mg Fertig
Enbrel
Etanerce
25 mg Fertigspritze
Enbrel® 25 mg
Injektionslösung in Fertigspritze
Etanercept
Pfizer


50mg
Enbrel
etanercept
エンブレル 皮下注50mg ペン 1.0mL
50mg
50mg
2キット
Pfizer


50 mg Fertig
Enbrel
Etanerce
25 mg Fertigspritze
Enbrel® 25 mg
Injektionslösung in Fertigspritze
Etanercept
Jede Fertigspritze mit Enbrel enthält 25 mg Etanercept.
Die sonstigen Bestandteile in Enbrel sind:
Sucrose, Natriumchlorid, Argininhydrochlorid,
Natriumdihydrogenphosphat-Dihydrat,
Natriummonohydrogenphosphat-Dihydrat und Wasser für
Injektionszwecke.
Injektionslösung in Fertigspritze
4 Fertigspritzen
8 Alkoholtupfer
Subkutane Anwendung.
Packungsbeilage beachten.
Hinweis für die Injektion:
Injizieren Sie die Lösung, nachdem sie Raumtemperatur erreicht
hat (15 bis 30 Minuten nach Entnahme aus dem Kühlschrank).
Injizieren Sie langsam in einem Winkel zwischen 45° und 90°
zur Haut.
Arzneimittel für Kinder unzugänglich aufbewahren.
Im Kühlschrank lagern.
Nicht einfrieren.
Die Fertigspritzen im Umkarton aufbewahren, um den Inhalt vor
Licht zu schützen.
Pfizer


Enbrel
etanercept

Aliaa Omar El-

.youtube.com/watch?v=52CLRN2gFYk

Enbrel - Injection training animation for correct usage.

YOUTUBE.COM

Nermeen Makram

ممكن حضرتك يا د علياء تقوليلنا تكلفة العلاج تقريباً

BIOLOGIC AGENTS - anti- TNF-α(9)
==========
2- Infliximab (Remicade):
==========
-Chimeric mouse–human monoclonal antibody composed of the constant regions of human IgG1 heavy and partial kappa light chain domains coupled to the variable region of a mouse light chain with high affinity for human TNF-α.

-Infliximab binds both soluble and cell bound TNF-α and thus has the ability to induce apoptosis of cells with TNF-α bound to its surface.

-It does not bind lymphotoxin.

-Its half-life is 8 to 9 days.

-Concomitant use of methotrexate (MTX) increases the amount of infliximab exposure by 30%.

• Available formulations:
single use vials of 100 mg.

• Dosage:

- RA: loading dose 3 mg/kg intravenous (IV) at weeks 0, 2, and 6; then every 8 weeks.
Dose can be increased as high as 5 to 10 mg/kg every 4 to 8 weeks.

- PsA, AS: loading dose 5 mg/kg IV at weeks 0, 2, and 6; then every 6 weeks.
Dose can be increased as high as 5 to 10 mg/kg every 4 weeks.

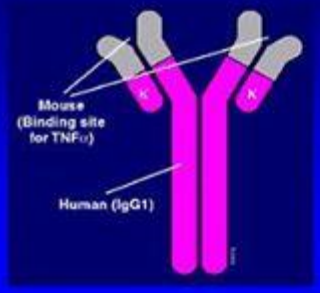
• Infusion takes 2 hours.

• In RA, typically used in conjunction with MTX or other synthetic DMARD to decrease development of human antichimeric antibodies (HACAs), which can neutralize/increase clearance of infliximab and/or cause infusion reactions.

Concomitant DMARD (MTX) use not needed for spondyloarthropathies because HACAs are much less likely to occur.

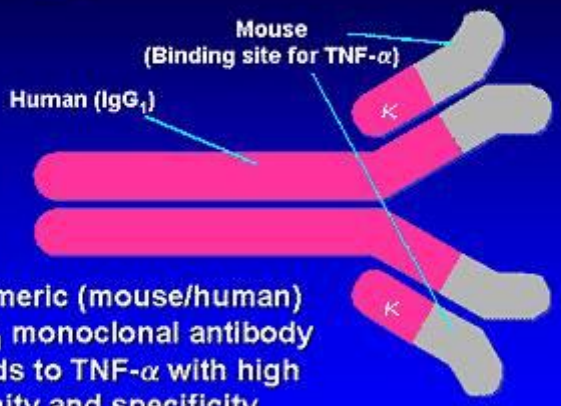
PEARL: if a patient is not responding initially, increasing the frequency of infliximab infusions is more efficacious than increasing the dose.
Rarely increase dose higher than 5 mg/kg every 4 weeks because of infection and malignancy concerns.

Remicade® (Infliximab)



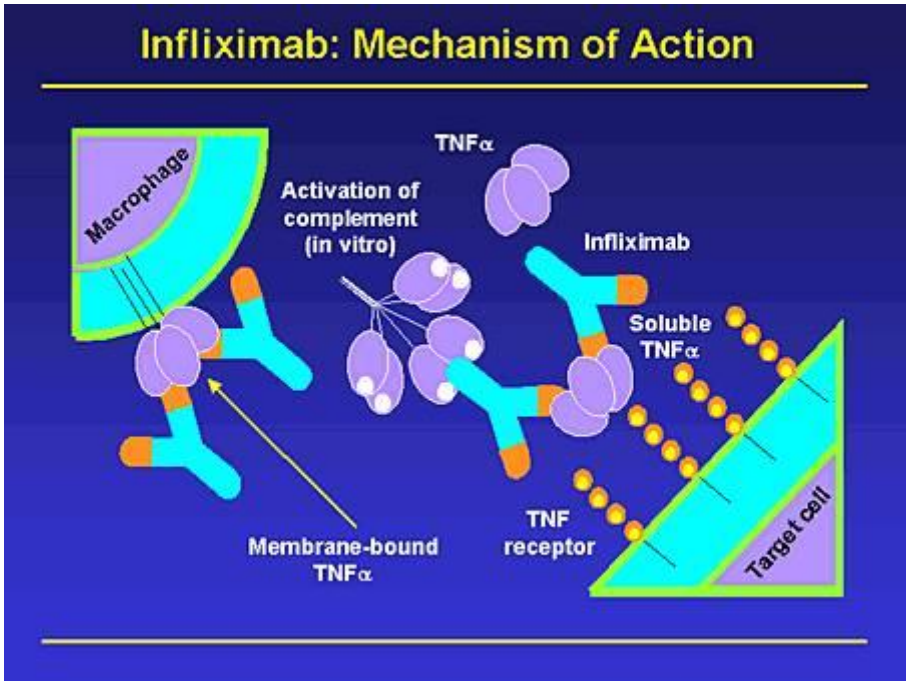
- Chimeric IgG1 monoclonal antibody
- High affinity binding to TNFα (Ka = $10^{10}M^{-1}$)
- Neutralizes only TNFα
- Highly stable complexes
- Selective lysis of activated TNFα expressing cells

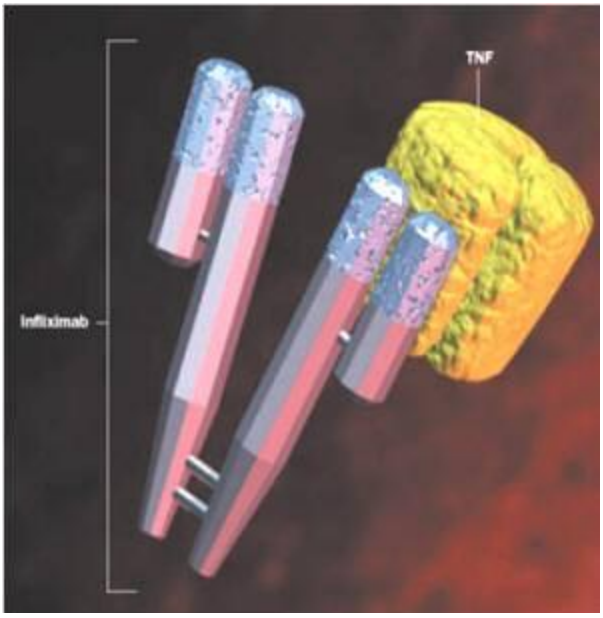
Infliximab



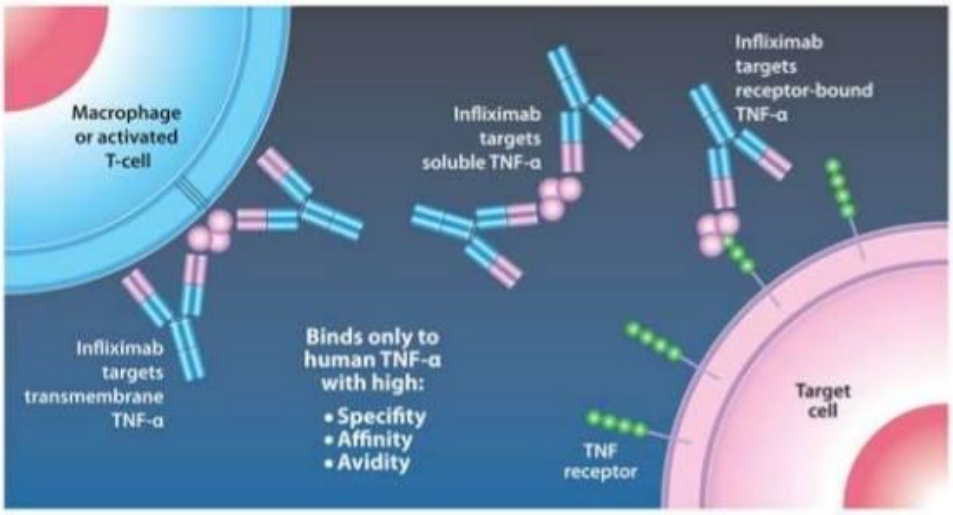
- Chimeric (mouse/human) IgG_1 monoclonal antibody
- Binds to TNF-α with high affinity and specificity

Knight DM, et al. *Mol Immunol.* 1993;30:1443-1453.


Infliximab: Mechanism of Action
Macrophage
Activation of complement (in vitro)
TNFα
Infliximab
Soluble TNFα
TNF receptor
Target cell
Membrane-bound TNFα


TNF
Infliximab

Infliximab (Remicade®▼) MODE OF ACTION



0.9% SODium CHLoride 250 mL
Primed for use with
Infliximab (REMICADE)

DILUENT: 250 mL 0.9% SODium CHLoride

IV SET: Primary Set (Alaris 2420-0500)

FILTER: 1.2 micron (Hospira 11415-05)

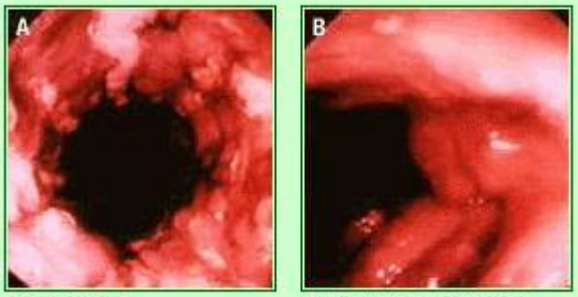
STORE IN REFRIGERATOR

This label represents just the primed bag.
Do not administer without a medication label.

PREP: 11/23/2013 17:02
DO NOT USE AFTER: 11/24/2013 17:02

PREP: _____
CHK: _____

Endoscopic Improvment With REMICADE® (infliximab)



Pretreatment | 4 Weeks posttreatment

Reprinted with permission of van Duffenn HM et al. Gastroenterology. 1996;109:129-135

FIGURE 2: A. Prior to treatment; B. Two weeks after the first dose; C. After eight weeks of treatment; D. After 10 weeks of treatment

Before After Treatment Photos

LifeForce HOMEOPATHY

Psoriasis on palms

Before After

Palmar Psoriasis
Courtesy of: G. Leone MD - IFO - (Rome - Italy) - A. Alomar et al. - Hospital de la Santa Creu i Sant Pau (Barcelona - Spain)

BIOLOGIC AGENTS - anti- TNF-α(10)
==========
3- Adalimumab (Humira):
==========
-Fully human IgG1κ monoclonal antibody that binds soluble and transmembrane forms of TNF-α. Its half-life is 10 to 13 days.

-Simultaneous use of MTX increases a patient's exposure to adalimumab by 30%.

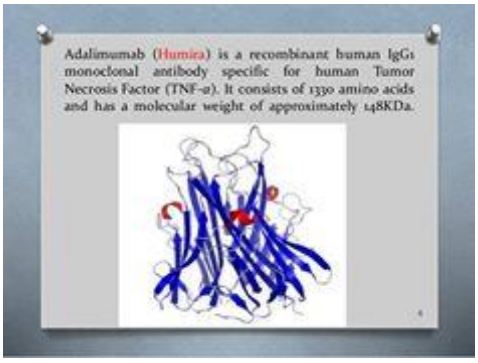
• Available formulations:
single use 40-mg prefilled syringe; single use 40-mg autoinjector pen. فيديو اول كومنت

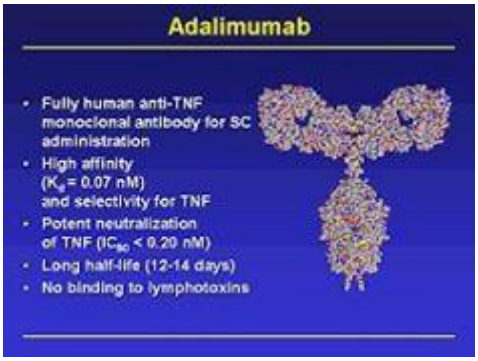
• Dosage: RA, PsA, AS: 40 mg SC every other week.

• Although approved for use as monotherapy, adalimumab works better in association with MTX in RA.

Some patients who do not respond to every other week dosing may respond to weekly dosing, although this is unusual and expensive.


Do not accept if seal on top of carton is broken or missing.
One 40 mg Vial
NDC 0074-3797-01
40 mg/ 0.8 mL
Humira®
Adalimumab
40 mg/0.8 mL
For Subcutaneous Use Only
Single-Use Vial
Discard Unused Portion
For Institutional Use Only
ATTENTION PHYSICIAN:
Each patient is required to receive the enclosed Medication Guide
Rx only
abbvie


Adalimumab (Humira) is a recombinant human IgG1 monoclonal antibody specific for human Tumor Necrosis Factor (TNF-α). It consists of 1330 amino acids and has a molecular weight of approximately 148KDa.


Adalimumab
Fully human anti-TNF monoclonal antibody for SC administration
High affinity (K_d = 0.07 nM) and selectivity for TNF
Potent neutralization of TNF (IC_{50} < 0.20 nM)
Long half-life (12-14 days)
No binding to lymphotoxins


HUMIRA 40 mg

Aliaa Omar El-

.youtube.com/watch?v=F9eJVYNP5C0

How to inject the Humira pen,"The most painful 10…

YOUTUBE.COM

BIOLOGIC AGENTS - anti- TNF-α(11)
==========
4- Golimumab (Simponi):
==========
-Fully human IgG1κ monoclonal antibody that binds soluble and transmembrane forms of TNF-α.

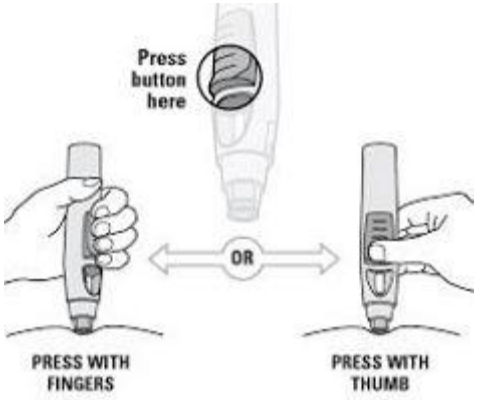
-Median half-life is 14 days.

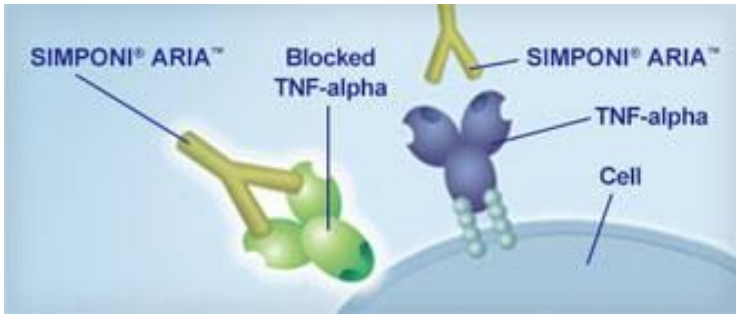
-Concomitant MTX use increases trough concentrations of golimumab by 30%.

• Available formulation:
single use 50-mg prefilled syringe; single use 50-mg SmartJect autoinjector; single use vials (50 mg/4 mL) for IV use.

• Dosage:
RA, PsA, AS: 50 mg SC once a month.
Simponi Aria: an IV formulation (2 mg/kg at 0, 4, then every 8 weeks) is approved for RA.

• Although SC formulation is prescribed as a once a month dose, some patients do not get a full month of benefit.
فيديو فى اول كومنت مش بالانجليزى ولكن مفهوم عن طريقة الحقن





Aliaa Omar El-hady https://www.youtube.com/watch?v=UO8ftTdlP2M

Golimumab (Simponi)

Administración de fármacos biológicos: Golimumab (Simponi)
Más información en ht…
YOUTUBE.COM

BIOLOGIC AGENTS - anti- TNF-α(12)

==========

5- Certilizumab pegol (Cimzia):

==========

-Fab fragment of a recombinant, humanized anti-TNF monoclonal antibody that has been fused to a polyethylene glycol (PEG) moiety.

-Cannot bind to Fc receptors, fix complement,or cross placenta due to not having a functional Fc fragment. هاااااااااااااااام

-Its half-life is 14 days.

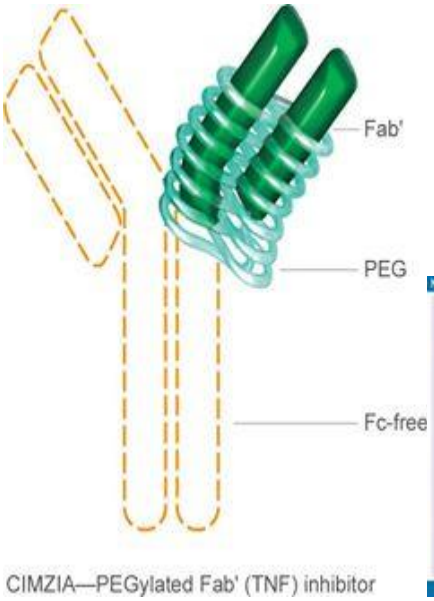
-The pegylation delays clearance and may help localize the molecule to acidic, inflammatory sites.

• Available formulation:
single use 200-mg prefilled syringe with specially designed grip.

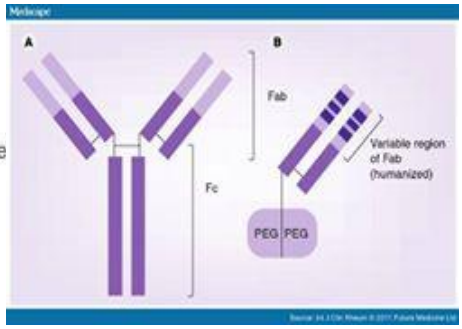
• Dosage:
RA, PsA, AS: loading dose 400 mg (two syringes) SC at weeks 0, 2, and 4; then 200 mg every 2 weeks.

• Owing to lack of functional Fc fragment, may be less injection site reactions and safer during pregnancy (does not cross placenta).
هاااااااااااااااااااااااام .... بيتاخد فى الحوامل

فيديو كيف نعطيه فى اول كومنت مش بالانجليزى ولكن مفهوم



CIMZIA—PEGylated Fab' (TNF) inhibitor



Aliaa Omar El-hady https://www.youtube.com/watch?v=a-

Certolizumab (Cimzia)

Administración de fármacos biológicos: Certolizumab (Cimzia) Más información en h…

YOUTUBE.COM

BIOLOGIC AGENTS - anti- TNF-α(13)

==========

How effective are TNF inhibitors in inflammatory arthritis?

==========

-TNF inhibitors have an onset of action within days to weeks.

-Most patients will achieve their maximum improvement within 3 months, although some continue to improve with continued use.

The following effects have been observed:

==========

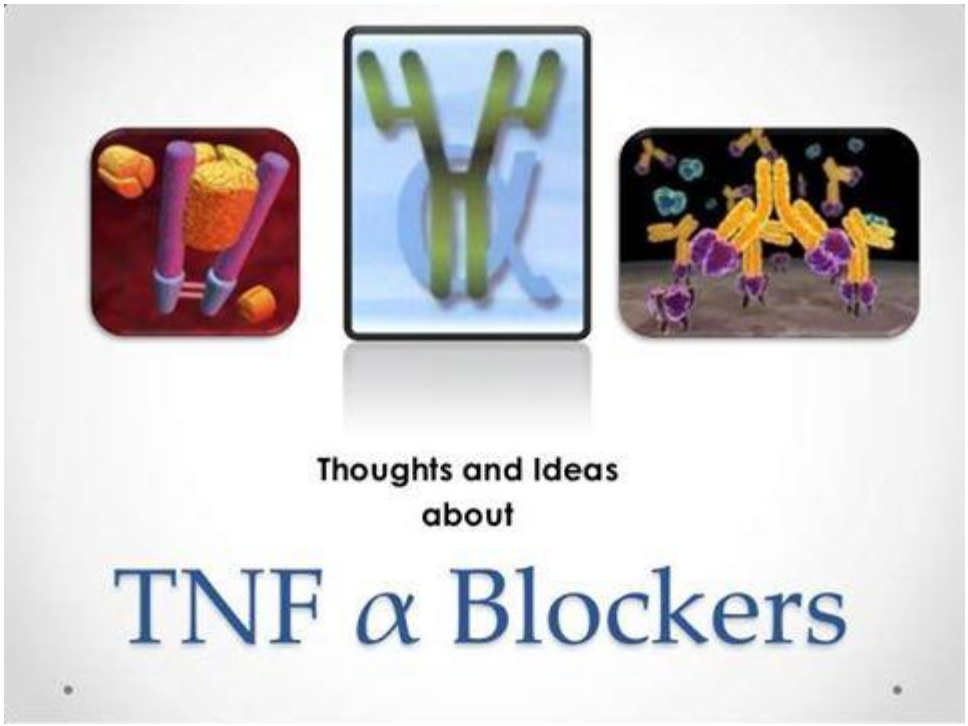
1• Disease activity (RA, PsA MTX inadequate responders):
60% of patients achieve an ACR 20; 40% an ACR 50; and 20% an ACR 70.

2• Psoriasis skin scores as measured by PASI (Psoriasis Area and Severity Index) improve more with infliximab than other TNF inhibitors.

3• Disease activity (patients with AS):
60% of patients achieve an ASAS (Ankylosing Spondylitis Disease
Activity Score) 20; 40% achieve an ASAS 40.

4• Radiographic joint damage is inhibited in RA and PsA.
Syndesmophyte formation is not inhibited in AS unless TNF inhibitors are started before they start to form. Once formed they may progress in spite of therapy over the first few years.
هاااااااااااااااااااااااااااااام جدا

5• Patients with inflammatory arthritis treated with TNF inhibitors have increased functionality, are more likely to stay employed, and have less cardiovascular mortality. This makes them cost effective with the number needed to treat being two at a cost of $30,000 to $50,000/QALY (quality-adjusted life year).



Aliaa Omar El-hady

BIOLOGIC AGENTS - anti- TNF-α(14)

==========

What are some of the side effects observed with anti-TNF-α biologic agents? How can these toxicities be limited?

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1. Injection site and infusion reactions:

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• All injectable TNF inhibitors:

injection site reaction (up to 50% of patients) lasting 3 to 5 days.
Some cause “bee sting” pain due to the preservative in the liquid. Treat with topical steroid or antihistamine.
Rotate the injection sites.
Usually reactions stop after 3 months of continued use.
If problems persist,lyophilized etanercept or certilizumab pegol can be used which seem to have fewer injection site reactions.

• Infliximab:

infusion reactions such as hypotension, headache (20%), nausea (15%), and dyspnea.
Treat by stopping the infusion and restarting at a slower rate.
If the patient has more than three drug allergies or has an infusion reaction, premedicate with Allegra (180 mg) 45 minutes before infusion; may also premedicate with aspirin (better than acetaminophen) and, if necessary, Solu-Cortef (100 to 125 mg IV).


Medscape®
www.medscape.com
Source: Dermatitis © 2006 American Contact Dermatitis Society

BIOLOGIC AGENTS - anti- TNF-α(16)

The side effects observed with anti-TNF-α biologic agents (cont.)

3. Malignancy:

TNF is important for inducing apoptosis in tumor cells. However, it is unclear if TNF inhibitors increase the risk of malignancy, particularly lymphoma.

Studies vary and state that the relative risk may (<5× relative risk) or may not be increased for lymphoma. However, most large studies report that it is not increased over the increased baseline risk of lymphoma associated with the underlying autoimmune disease being treated.

Children treated with TNF inhibitors may have an increased lymphoma risk.

Solid tumors are not increased.

Melanoma and other skin cancers may be increased.

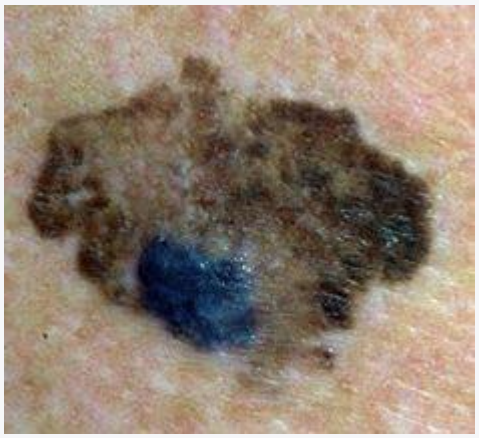
Patients who develop a cancer (other than melanoma) while receiving a TNF inhibitor do not have worse histology, more widespread disease, or worse prognosis.

Whether or not patients with active cancer or recently treated cancer can safely receive a TNF inhibitor is controversial, although it should not be used in patients with melanoma or lymphoma.

Many experts recommend not starting these agents until a patient is cancer free for 5 years.

FIGURE 1: Anterior view of tumor in the proximal region of right thigh and psoriatic lesions

Aliaa Omar El-hady melanoma



BIOLOGIC AGENTS - anti- TNF-α(17)

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The side effects observed with anti-TNF-α biologic agents (cont.)

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4. Demyelinating syndromes

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Brain demyelination (multiple sclerosis-like), optic neuritis, Guillain–Barré syndrome, polyradiculopathy, and peripheral demyelinating neuropathy have been reported rarely.

Most are reversible when the TNF inhibitor is stopped.

Therefore, TNF inhibitors should not be given to patients with a history of multiple sclerosis or optic neuritis.

Some experts recommend brain MRI in patients with a strong family history of demyelinating disease to look for occult lesions.

If silent lesions are present do not give the patient TNF inhibitors.

---

5. Autoimmune phenomenon

==========

Between 10% and 50% of patients on TNF inhibitors will develop a positive antinuclear antibody, 10% to 15% develop anti-dsDNA antibodies (IgM isotype), and a small number (0.2% to 0.4%) develop drug-induced lupus (DIL).

A few patients have developed antiphospholipid antibodies and antineutrophil cytoplasmic antibodies (ANCAs) that are rarely clinically significant.

Patients who develop DIL have mild symptoms of arthritis, rash, and serositis that resolves with TNF inhibitor discontinuation.

Small vessel leukocytoclastic vasculitis has rarely been reported.

Infliximab is more likely to cause these autoimmune phenomena than other TNF inhibitors.

Concomitant use of MTX does not lessen the frequency of these manifestations.

• Antidrug antibodies:

==========

over 20% of patients treated with infliximab will develop HACAs.

Patients who develop HACAs may lose their response to infliximab (i.e., neutralizing antibodies) and/or experience more severe infusion reactions.

Concomitant MTX therapy in RA patients (not spondyloarthropathy patients) is recommended to decrease the risk of developing HACAs.

Less than 10% of patients receiving SC formulations of TNF inhibitors develop antidrug antibodies.

This is decreased to less than 1% with concomitant MTX use.

These antibodies are rarely neutralizing but may bind and increase the clearance making the TNF inhibitor less effective.

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6. Congestive heart failure

==========

Avoid TNF inhibitors (especially infliximab) in patients with class III or class IV congestive heart failure (CHF).

---

7. Hematologic

==========

Neutropenia, thrombocytopenia, and pancytopenia have rarely been reported. Monitoring with periodic CBC (every 3 months) is recommended.

---

8. Others

==========

Sarcoidosis,
subacute cutaneous lupus-like rash,
seizures,
colonic perforations,
increased liver enzymes >3-fold elevation (2% to 4%),
severe hepatotoxicity (rare but most common with infliximab),
and noninfectious pulmonary infiltrates have been reported.

• Palmoplantar psoriasis:
less than 1% develop worsening psoriasis on palms and soles. Not prevented by using MTX. Etiology unknown but may be attributable to increased IFN-α production.

Patients with SAPHO or pustular psoriasis are more likely to get this with infliximab.


1

BIOLOGIC AGENTS - anti- TNF-α(18)

==========

Q- Can more than one TNF inhibitor be tried in a patient?
Are there any useful switching “rules”?

==========

Most physicians and patients feel that at least a 50% overall clinical response is necessary to justify the cost and risk of using a TNF inhibitor.

At least 50% of patients with RA, AS, or PsA may not achieve this response or will develop an intolerance to the first TNF inhibitor they are put on.

Although controversial, most physicians will try a second TNF inhibitor.

The effectiveness of switching TNF inhibitors and the “rules” for switching can be summarized as follows:

==========

• Patients who fail to respond to the first TNF inhibitor (primary failures) are less likely to get a good response to a second TNF inhibitor compared to patients who initially responded to a TNF inhibitor and then lose that response (secondary failures) or who had to stop the TNF inhibitor as a result of an adverse event (intolerance).

Only 4% to 5% of primary failures will get a good response to a second TNF inhibitor compared to 27% to 30% of patients who had secondary failure/intolerance.

• Patients who had an adverse event to their first TNF inhibitor are more likely (2 to 3 times) to develop an adverse event to a second TNF inhibitor.

• To increase the chance of a response in a primary failure patient, choose a second TNF inhibitor which is a different molecule. For example, if the patient fails adalimumab (monoclonal antibody), put them on etanercept (soluble receptor) and vice versa.

Some patients may respond well to certolizumab pegol which is a pegylated molecule even if they failed a TNF inhibitor that was a monoclonal antibody.

• Patients who are secondary failures or have developed adverse events to a TNF inhibitor (especially infliximab) may have developed neutralizing antibodies, and switching to a second TNF inhibitor of any type can be beneficial.

• If a patient has a primary failure to two TNF inhibitors, there is probably no benefit to try a third.

There are some clinical trial data to suggest that patients who have failed two or more TNF inhibitors may still respond to certolizumab attributable to its unique formulation (controversial).

BIOLOGIC AGENTS - IL-1 inhibitors (19) المجموعة التانية
==========
What biologic agents are currently available to inhibit IL-1?
==========
1- Anakinra (Kineret):

-a recombinant, nonglycosylated form of the human IL-1 receptor antagonist (IL-1Ra).

-It blocks the biologic activity of IL-1 by competitively inhibiting IL-1 binding to the IL-1 type I receptor.

-The half-life is 4 to 6 hours.

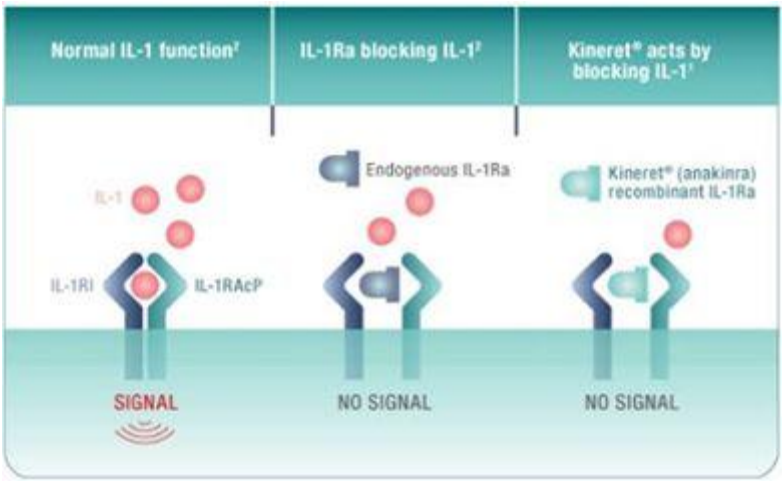
2- Rilonacept (Arcalyst):

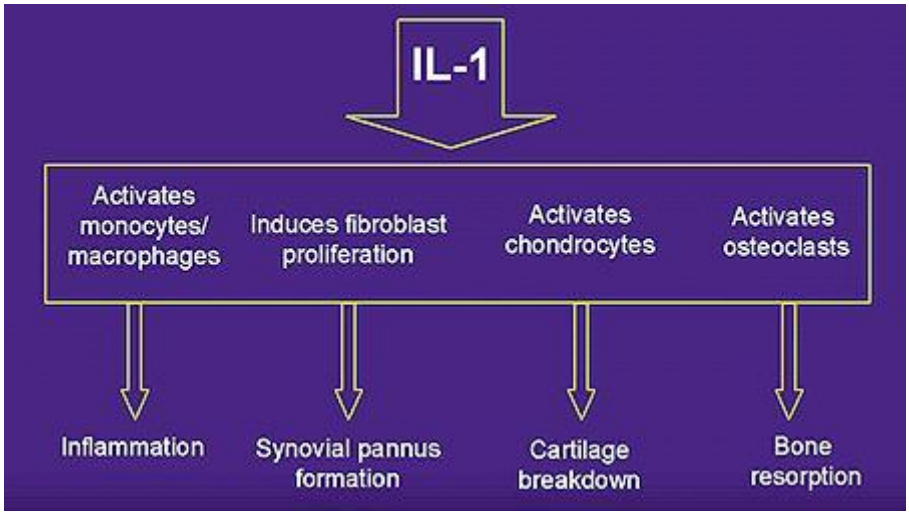
-dimeric fusion protein that incorporates in a single molecule the extracellular domains of both IL-1 receptor (IL-1R) and IL-1 receptor accessory protein (IL-1RAcP) fused to the Fc portion of an
IgG1 molecule.

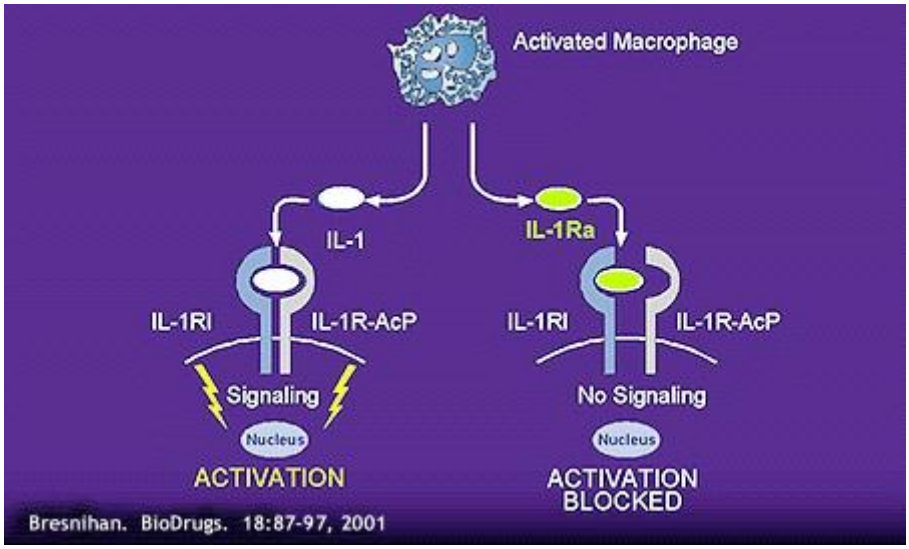
-Targets both IL-1α and IL-1β. Also known as IL-1 TRAP.

3- Canakinumab (Ilaris):
---
human monoclonal antibody that specifically targets IL-1β.


sobi
Kineret® 100 mg
Injektionslösung in einer Fertigspritze
Solution injectable en seringue préremplie
Oplossing voor injectie in een voorgevulde spuit
Anakinra
x7

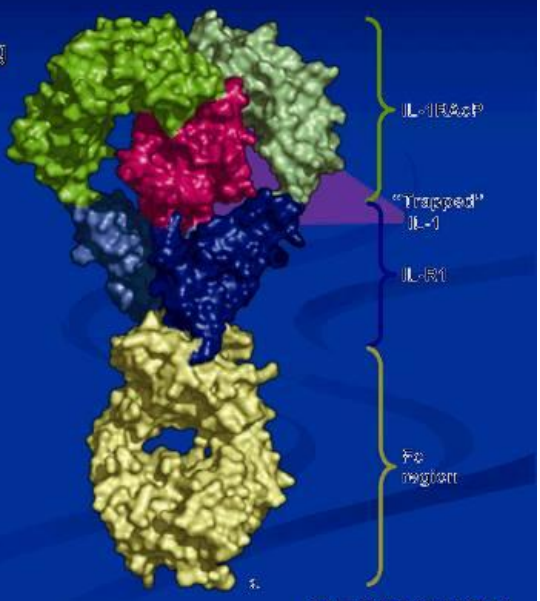

Normal IL-1 function[2]
IL-1Ra blocking IL-1[2]
Kineret® acts by blocking IL-1[1]
IL-1
IL-1RI
IL-1RAcP
Endogenous IL-1Ra
Kineret® (anakinra) recombinant IL-1Ra
SIGNAL
NO SIGNAL
NO SIGNAL


IL-1
Activates monocytes/ macrophages
Induces fibroblast proliferation
Activates chondrocytes
Activates osteoclasts
Inflammation
Synovial pannus formation
Cartilage breakdown
Bone resorption



Rilonacept (ARCALYST®): Structure and Characteristics

- Rilonacept: a dimeric fusion protein
  - Specific blocker of IL-1, incorporating extracellular domains of the 2 receptor components required for IL-1 signalling
    - IL-1RI (IL-1 receptor sub-type 1)
    - IL-1RAcP (IL-1 receptor accessory protein)
  - Molecular weight ~251 kDa
  - Expressed in recombinant Chinese hamster ovary (CHO) cells
- 8.6 days circulation half-life *in vivo*, allowing for once-weekly dosing



REGENERON


NDC 61755-001-01
Arcalyst™
(rilonacept)
Injection for Subcutaneous Use
220 mg sterile powder for reconstitution
Store at 2-8°C (36-46°F) until use. Protect from light.
Contents: four (4) single-use vials
REGENERON
℞ ONLY
3ml


ILARIS
(canakinumab)

BIOLOGIC AGENTS - IL-1 inhibitors (20) المجموعة التانية

==========

Anakinra (Kineret)

==========

• Available formulation: single use vial of 100 mg.

• Dosage: 100 mg SC daily.

• Follow-up: CBC monthly for 3 months, then every 3 months.

• Adverse reactions: serious infections (2%), neutropenia (3%).

• Injection site reactions (70%): less likely if ice is placed on skin before injection. Treat with topical steroids.

• Precautions: do not use in patients with active infection. Do not combine with other biologics.

• FDA-approved indication:
RA,
neonatal onset multisystem inflammatory disease (NOMID).

• Other diseases that it has been used with success:
Still's disease,
gout,
familial Mediterranean fever,
cryopyrin-associated periodic syndromes (CAPS).

• Cost: $1500 per month.

BIOLOGIC AGENTS - IL-1 inhibitors (21) المجموعة التانية

Rilonacept (Arcalyst)

- Available formulation: single use, glass vial containing 220 mg of lyophilized powder for reconstitution.
- Dosage.

Ages 12 to 17 dose:
load with one dose 4.4 mg/kg (maximum 320 mg) followed by 2.2 mg/kg (maximum 160 mg) SC weekly.

Adult dose:
load with one dose 320 mg followed by 160 mg SC weekly.

- Follow-up: CBC periodically. Get lipid profile at 3 months.
- Adverse reactions:
injection site reaction (48%), infections (25%), serious infections (rare), other common symptoms.
- Precautions: do not use in patients with active infection; warfarin interaction.
- FDA-approved indication: CAPS (familial cold autoinflammatory syndrome [FCAS], Muckle–Wells syndrome [MWS]).
- Other diseases that it has been used with success: gout, Still’s disease, other cryopyrinopathies (CAPS).
- Cost: $24,000 per month.


NDC 61755-001-01
Arcalyst™
(rilonacept)
Injection for Subcutaneous Use
220 mg sterile powder for reconstitution
Store at 2-8°C (36-46°F) until use. Protect from light.
Contents: four (4) single-use vials
℞ ONLY
REGENERON
3ml
2½
2
1½
1
½

BIOLOGIC AGENTS - IL-1 inhibitors (22) المجموعة التانية
==========
Canakinumab (Ilaris)
==========
• Available formulation: glass vial containing 180 mg of lyophilized powder for reconstitution.

• Dosage.

Patient weight 15 to 40 kg: 2 to 3 mg/kg SC every 8 weeks.
Patient weight >40 kg: 150 mg SC every 8 weeks.

• Follow-up: CBC and hepatic enzymes periodically.

• Adverse reactions: nasopharyngitis, diarrhea, vertigo (10%), headache, injection site reactions (9%),other common symptoms.

• Precautions: do not use in patients with active infection; warfarin interaction.

• FDA-approved indication: CAPS (FCAS, MWS), systemic JIA (Still's disease).
• Other diseases that it has been used with success: gout, other cryopyrinopathies (CAPS).

• Cost: $8000 per month.

BIOLOGIC AGENTS - IL-6 inhibitors (23) المجموعة الثالثة
==========
Tocilizumab (Actemra)
==========
-Is a humanized IgG1κ monoclonal antibody that binds to the soluble and membrane bound forms of the IL-6 receptor (IL-6R).

-This antibody inhibits IL-6 signaling of cells that constitutively express IL-6R as well as cells that bind the soluble form of IL-6R that interacts with gp130 on a wide variety of cells.

- Half-life is 8 to 14 days depending on dose.

-MTX does not help to increase the exposure to tocilizumab. It is controversial whether or not tocilizumab is more effective when used in combination with MTX.

• Available formulation:
---
80 mg, 200 mg, 400 mg single use vials for IV administration; prefilled (1 mL) ready to use, single use syringe.

• Dosage.

RA: 4 mg/kg IV once every 4 weeks as a 60-minute infusion. Can increase to 8 mg/kg IV (not to exceed 800 mg) monthly if needed.

• SC formulation:
if >100 kg body weight 162 mg SC weekly;
if <100 kg body weight 162 mg SC every other week.
If not effective the dose can be increased to weekly.

• Systemic JIA (Still's disease):
patient weight <30 kg: use 12 mg/kg IV monthly;
>30 kg: use 8 mg/kg IV monthly.

• Tocilizumab can be used with or without MTX or another DMARD.

• Monitoring:

CBC (with differential) and hepatic enzymes monthly until stable dose, then every 1 to 2 months.

Lipid panel every 1 to 2 months until stable dose, then every 6 months.

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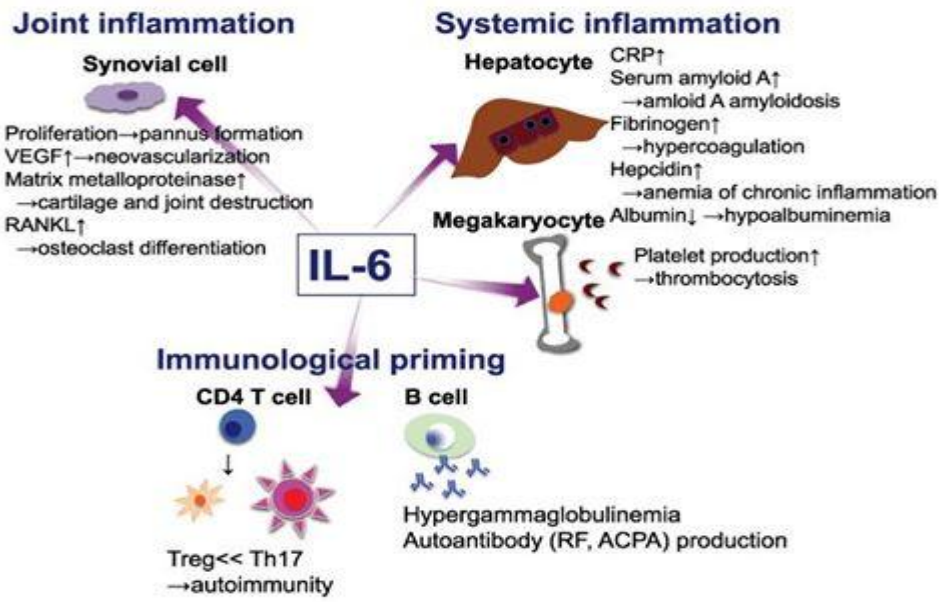

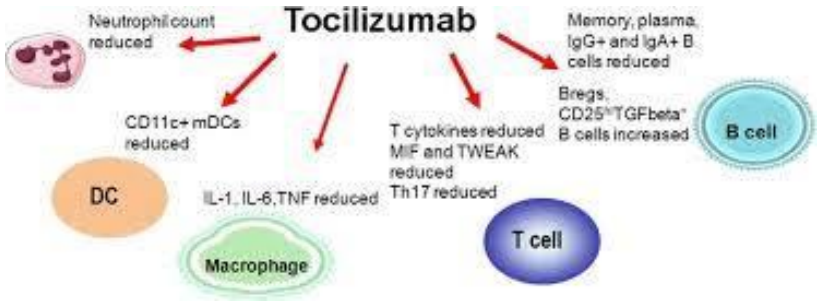

BIOLOGIC AGENTS - IL-6 inhibitors (24) المجموعة الثالثة
==========

Tocilizumab (Actemra) cont.
==========

• Adverse reactions: امهاااااااااااااا

all adverse events more common on 8 mg/kg than 4 mg/kg dose.

• Infusion reactions (8%):
headaches, hypertension. Premedication usually not necessary. Serious reactions rare.

• Infections:
upper respiratory (8%), serious infections (3 to 5 events/100 patient years), Herpes zoster,opportunistic (rare).

• Elevated hepatic enzymes: امهاااااااااااااااا

---

attributable to binding IL-6R on liver cells which blocks antiapoptotic effects of IL-6 on liver cells.

• Enzymes between 1 and 3 times upper limit normal (ULN) (35% to 50% of patients): reduce tocilizumab dose and/or modify DMARD (MTX) dose.

• Enzymes >3 to 5 times ULN (5%): stop tocilizumab until enzymes <3times ULN, then restart at lower dose and/or modify DMARD dose.

• Enzymes >5 times ULN (0.5% to 1.5%): discontinue tocilizumab.

• Neutropenia (29%):

---

as a result of binding IL-6R on neutrophils.

• Absolute neutrophil count (ANC) >1000/mm3:continue tocilizumab.

• ANC 500 to 1000/mm3 (2% to 4% of patients): stop tocilizumab until ANC >1000/mm3, then restart at lower dose.

• ANC <500/mm3 (0.4%): discontinue tocilizumab.

• Thrombocytopenia (8%): discontinue if <50,000/mm3 (0.1%).

• Lipid elevations:
---
mean increase low-density lipoprotein (LDL) was 10 to 20 mg/dL and mean high-density lipoprotein (HDL) increase was 3 to 5 mg/dL.

• Gastrointestinal perforations (0.26 events/100 patient years): IL-6 important for fibrotic healing and repair of GIT inflammation.

• Macrophage activation syndrome: seen in 3% of systemic JIA patients treated with tocilizumab.

• No increase in malignancy, CHF, or demyelinating disease noted. Patients with hepatitis B were excluded from trials and thus reactivation risk is unknown.

• Precautions:
---
do not use in:
patients with active infection,
hepatic enzymes >1.5× upper limit,
platelet count <100,000/mm3,
history of diverticulitis or other inflammatory bowel disease.

Drug interactions include affecting blood levels of
---
warfarin, cyclosporine, and theophylline.
Lowers blood levels of omeprazole, simvastatin, and birth control pills. Advise patients about birth control.

• FDA-approved indications: RA and systemic JIA (Still's disease).
• Other diseases that it has been used with success: Castleman's disease, giant cell arteritis, Takayasu's arteritis,relapsing polychondritis, adult-onset Still's disease, SLE.

Does not work for spondyloarthropathies. هاااااااااااااااام


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BIOLOGIC AGENTS - Ustekinumab (Stelara) - (25)
==========
What is ustekinumab (Stelara) and why is it effective in psoriatic arthritis?

Ustekinumab is a human IgG1κ monoclonal antibody that binds to the p40 subunit of both IL-12 and IL-23 preventing their binding to their shared cell surface receptor chain, IL-12β.

The inhibition of IL-12 signaling abrogates Th1 response with reduction in TNF-α, IFN-γ, and IL-2 production.

The inhibition of IL-23 signaling abrogates Th17 response with reduction in IL-6, IL-17, IL-21, IL-22, and TNF-α production.

Th17 cells and IL-23 production by dendritic cells and keratinocytes are important in the pathogenesis of psoriasis.

Half-life is 15 to 45 days.

• Available formulation:
single use 45-mg and 90-mg prefilled syringes or vials.

• Dosage.
psoriasis or PsA:

patient ≤100 kg: 45 mg SC initially, followed by 45 mg in 4 weeks, then 45 mg every 12 weeks.

Dosage for >100 kg: 90 mg SC initially, followed by 90 mg in 4 weeks, then 90 mg every 12 weeks.

• Monitoring:
routine monitoring for other DMARDs (MTX).

• Adverse reactions:
nasopharyngitis (10%), nonmelanoma skin cancers.

• Serious infections (2% to 3%):
IL-12/IL-23 are important for resistance against mycobacterial and
salmonella infections. IL-17 is important for resistance against fungal infections.

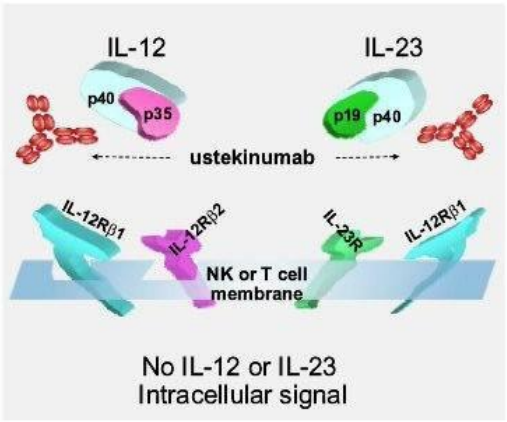
• Precautions: do not use in patients with active infection. Do not combine with other biologics.مالاااااااااااااااااها

• FDA-approved indications: psoriasis and psoriatic arthritis.

STELARA™ (ustekinumab)

First-in-class anti-IL-12/23 p40

- Novel, first-in class, dual mechanism of action
- Subcutaneous (SC) delivery
- Every 12 week dosing!
- Initial indication in psoriasis
  - Approved in Canada and EU
  - Filed in U.S. and 44 countries
- Excellent safety profile to date
- Ongoing long-term safety program
- Higher response rate than Enbrel® in comparator trial



No IL-12 or IL-23 Intracellular signal

Enbrel® is a registered trademark of Immunex Corporation.

Johnson & Johnson

BIOLOGIC AGENTS - Tofacitinib (Xeljanz)- (26)
==========

What is tofacitinib (Xeljanz)?

Tofacitinib is a novel oral DMARD which inhibits JAK.

The JAK proteins are intracellular proteins that associate with and transduce signals from a number of cytokine and growth factor receptors.

There are four JAKs that form various dimers with different pairings being associated with different cell surface receptors resulting
in the production of a variety of inflammatory mediators.

Tofacitinib acts on JAK1/JAK2 (important for IL-6 and IFN signaling), JAK1/JAK3 (important for T and B cell signaling), and JAK2/JAK2 (growth factor signaling) dimer pairs.

As a result of JAK 3 inhibition, the production of IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21,which are important in T and B cell activation and function, are decreased.

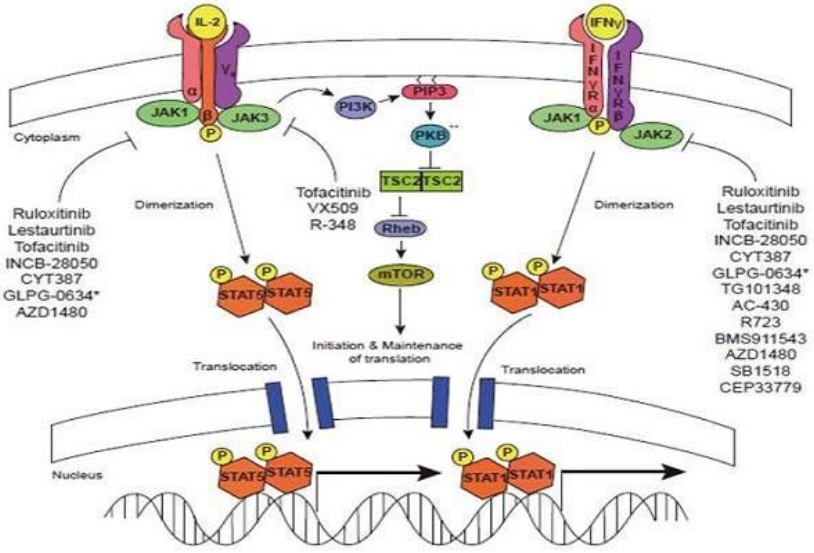
Additionally, with JAK1 inhibition,IL-6 and IFN-γ production are attenuated.

Finally IL-2-dependent differentiation of Th2 and Th17 cells is decreased.

It is metabolized and eliminated primarily by the liver (70%) with the remainder excreted by the kidneys (30%).

Half-life is short (3 hours).


ALWAYS DISPENSE WITH
MEDICATION GUIDE
NDC 0069-1001-01
Pfizer
Xeljanz®
(tofacitinib) tablets
5 mg*
60 Tablets
Rx only


IL-2
IFNγ
JAK1
JAK3
JAK2
PI3K
PIP3
PKB
TSC2
Rheb
mTOR
Cytoplasm
Dimerization
Dimerization
Tofacitinib
VX509
R-348
Ruloxitinib
Lestaurtinib
Tofacitinib
INCB-28050
CYT387
GLPG-0634*
AZD1480
Ruloxitinib
Lestaurtinib
Tofacitinib
INCB-28050
CYT387
GLPG-0634*
TG101348
AC-430
R723
BMS911543
AZD1480
SB1518
CEP33779
STAT5
STAT1
Initiation & Maintenance
of translation
Translocation
Translocation
Nucleus


JKI
5
Pfizer

BIOLOGIC AGENTS - Tofacitinib (Xeljanz)- (27)
==========
How is tofacitinib supplied and used? What are its toxicities?

• FDA-approved indication:
RA with inadequate response to MTX.

• Available formulation:
5-mg tablet.

• Dosage:
-5 mg twice a day.
-Not affected by food.
-Dose should be decreased to 5 mg daily if severe liver or renal disease.
-Can be given alone or in combination with MTX.
-Avoid azathioprine.

• Follow-up:
CBC (with differential), creatinine, and hepatic enzymes monthly for 3 months, then every 3 months.
Maximum effect on lipids occurs by 6 to 8 weeks, thus lipid panel should be done at that time.

• Adverse reactions:
common symptoms (4% to 5%) include nasopharyngitis, diarrhea, and headache.

• Infections: any (20%), serious (2.7 events/100 patient years), opportunistic (0.3 events/100 patient years). Herpes zoster may be increased more than with other biologics and DMARDs.

• Hematologic: lymphopenia <500/mm3 (0.3%), ANC <1000/mm3 (0.07%), or hemoglobin drop >2g/dL.
Stop tofacitinib until counts recover, then restart at lower dose.
Lymphopenia associated with higher infection rate.

• Hepatic enzyme elevations >3 × ULN (1.3%).
Stop tofacitinib until enzymes improve, restart at lower dose.

• Lipid abnormalities: LDL increases 15% and HDL increases 10%.

• Creatinine increase >50% (2% of patients): etiology unknown.
Discontinue tofacitinib.

• Malignancy: solid tumors (0.6 events/100 patient years) and lymphoma reported in tofacitinib group but not placebo-treated group.

• Gastrointestinal perforations: have been reported.

• Immunizations: decreases response to inactivated vaccines.

• Precautions: do not use in patients with active infection.

Patients with hepatitis B and hepatitis C excluded from trials.

Drug interactions include decreased effectiveness if used with rifampin.

The tofacitinib dose needs to be decreased by half if the patient is put on ketoconazole/fluconazole.

BIOLOGIC AGENTS - B cell targeted therapies- (28)
==========
1-Rituximab (Rituxan) (1):
==========
chimeric mouse–human IgG1κ monoclonal antibody directed against extracellular domain of CD20 antigen on B cells.

B cells are eliminated by complement-mediated lysis, antibody-dependent cell mediated cytotoxicity, or apoptosis.

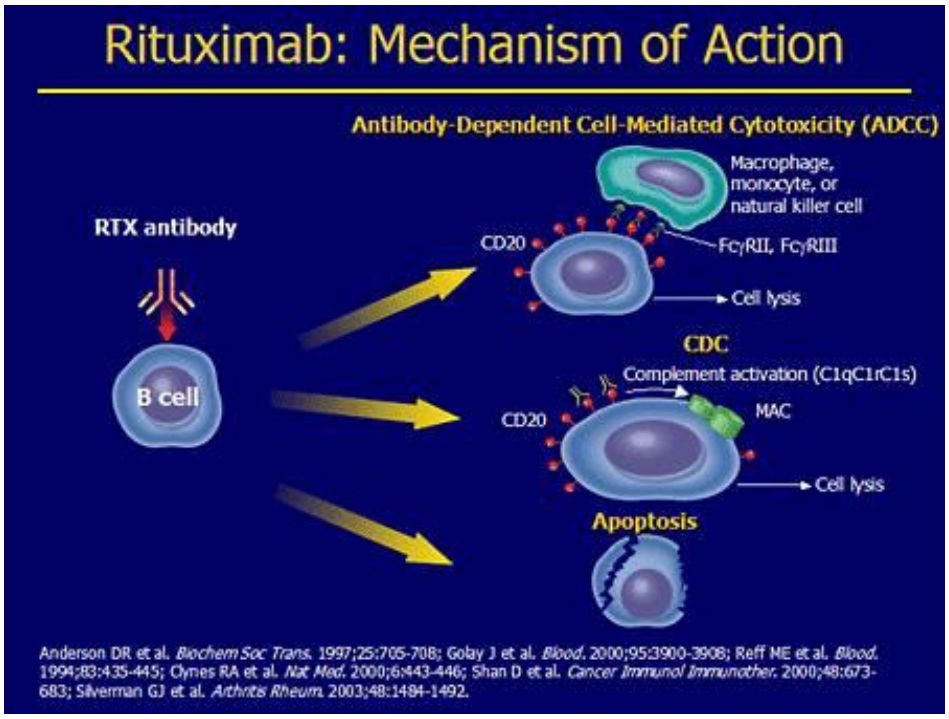
All peripheral B cells are eliminated within days.

Patients who fail to deplete their B cells respond less well.

Notably, Ig levels are preserved due to preservation of plasma cells
which lack the CD20 antigen on their cell membranes.

Repeated infusions can cause decreased Ig levels (IgM > IgG > IgA).

Half-life is 19 to 22 days.




RITUXAN®
NDC 50242-051-21
Rituximab
100 mg/10 mL (10 mg/mL)
For Intravenous Use
100 mg
℞ only
One 100 mg vial
Jointly Marketed by:
Biogen Idec Inc., and Genentech USA, Inc.
Rituximab
RITUXAN

BIOLOGIC AGENTS - B cell targeted therapies- (29)
==========
1-Rituximab (Rituxan) (2):
==========
What are the indications of rituximab (Rituxan)?

• FDA-approved rheumatologic indications:

RA after MTX and anti-TNF failure;
ANCA-associated vasculitis (granulomatosis with polyangiitis [GPA], microscopic polyangiitis [MPA]).

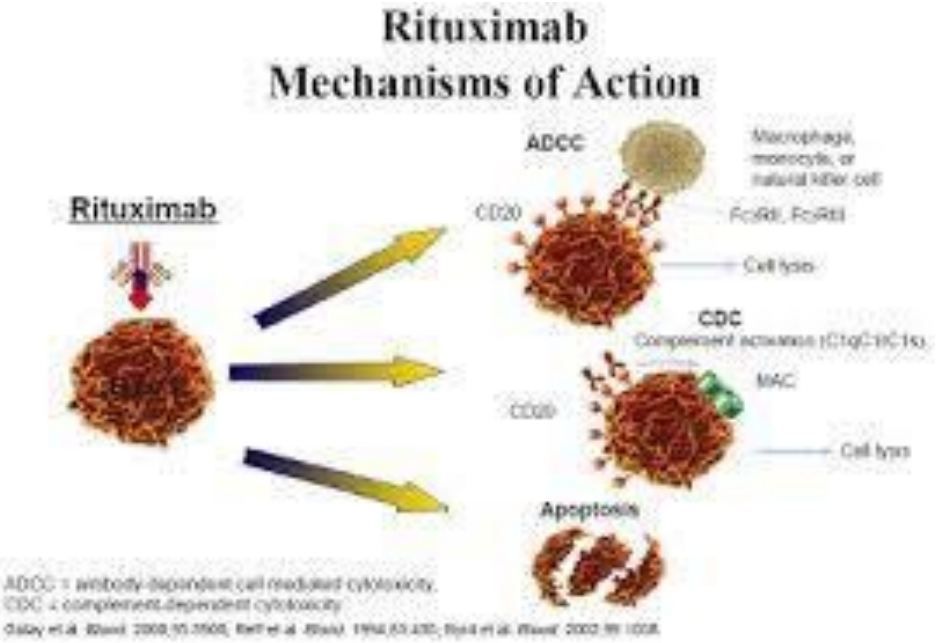
• Available formulation:
single use vial of 100 mg and 500 mg.

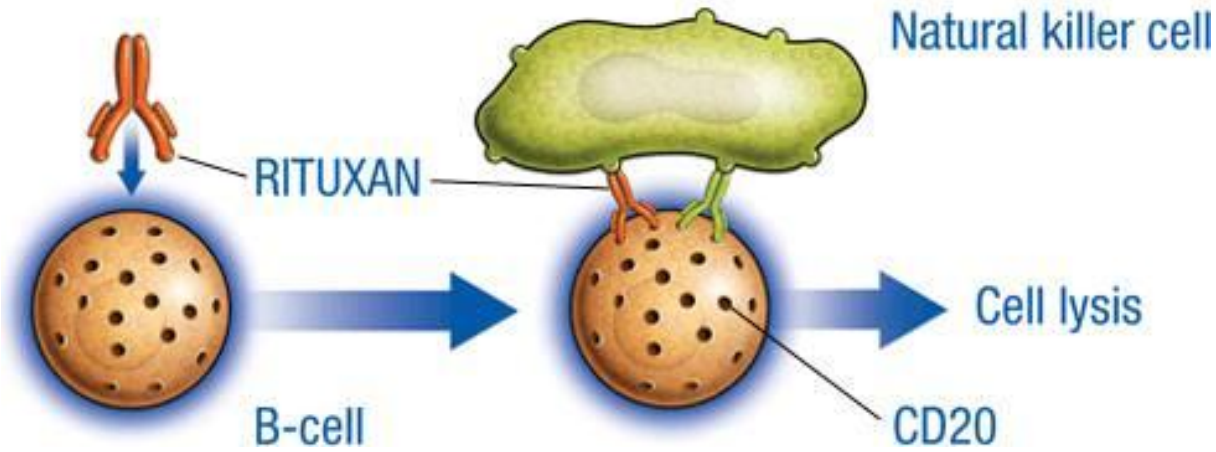
• Dosage. RA:
1000 mg IV infusion repeated once 2 weeks later.
Some physicians feel 500 mg dose is as effective as 1000 mg.
Can be used with concomitant DMARDs (MTX).

• ANCA-associated vasculitis:
375 mg/m2 IV infusion once weekly for 4 weeks.
Can also use RA dosage (1 g × 2).

• First infusion lasts 3 to 5 hours, subsequent infusions 2 to 3 hours.
Patients are typically premedicated 30 minutes before each infusion with solumedrol 100 mg, acetaminophen 1000 mg, and an antihistamine to decrease chance of infusion reaction.

• Follow-up:
CBC every 2 to 4 months to monitor for late-onset neutropenia.


Rituximab
Mechanisms of Action
Rituximab
ADCC
Macrophage, monocyte, or natural killer cell
CD20
FcγRI, FcγRII
Cell lysis
CDC
Complement activation (C1q/C1r/C1s)
MAC
CD20
Cell lysis
Apoptosis
ADCC = antibody-dependent cell-mediated cytotoxicity
CDC = complement-dependent cytotoxicity


Natural killer cell
RITUXAN
Cell lysis
B-cell
CD20

BIOLOGIC AGENTS - B cell targeted therapies- (30)
==========
1-Rituximab (Rituxan) (3):
==========
What are the toxicities of rituximab (Rituxan)?

• Infusion reaction (10% to 35%):
usually not severe if use premedication.
Respond to stopping infusion until symptoms gone, then restart at slower rate. Stop infusion if patients start clearing their throat due
to a scratchy feeling.

Serious reactions (1%). Risk does not increase with subsequent infusions. May not need premedication with subsequent infusion if tolerated well.

• Infection:
any (35% or 78 events/100 patient years); serious (2% or 3 events/100 patient years); opportunistic (0.05/100 patient years, very low rate).

• Viral infections: reactivation of resolved hepatitis B (HBsAg–, HBcAb+) occurs in 5% to 10%.

Patients with chronic and inactive hepatitis B (HBsAg+) should either not receive rituximab or must receive concomitant antiviral prophylaxis (lamivudine, other) starting 2 to 4 weeks before and continuing while on rituximab and for 1 month after stopping.

Patients with hepatitis C can receive rituximab without antiviral therapy but need hepatic enzyme and viral RNA load monitoring.

The risk of JC virus infection resulting in progressive multifocal leukoencephalopathy (PML) may vary by disease being treated and previous immunosuppressive medications (1:25,000 RA patients, 1:4000 SLE patients compared to 1:200,000 in the general population). Owing to frequency of JC virus exposure (60% to 70%) and low rate of PML in RA patients treated with rituximab, it is not recommended to screen patients with antibody testing for previous JC virus exposure. Herpes zoster

appears
increased.

• Hypogammaglobulinemia: only occurs in patients after multiple courses of rituximab therapy. IgG becomes low in 3.5% to 12% of patients, IgM low in 22% to 26%. Patients who develop low IgG more likely (2×) to get serious infection.

• Late-onset neutropenia: occurs in 3% of patients with RA and up to 20% of SLE or ANCA-associated vasculitis patients treated. Occurs an average of 3 to 4 months post-therapy and is associated with increased infection risk (16%). Cause is unclear. Tends to recur with subsequent doses.

• Immunizations: responses to killed vaccines are severely decreased if given after rituximab. Give 2-4 weeks before or 4 to 6 months post-rituximab infusion.

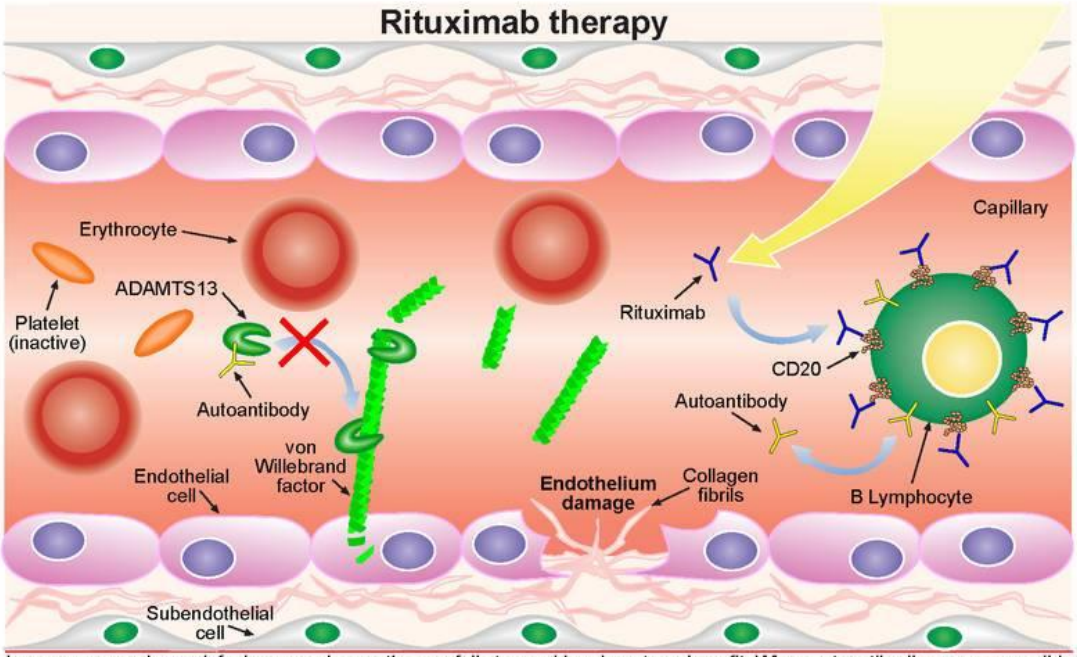
• Other: severe mucocutaneous reactions, hypertension/arrhythmias/myocardial infarction during infusions.

Note that CHF, demyelinating disease, malignancy (except skin cancer), and mycobacterial infections were not increased over placebo. Rituximab may be used ahead of TNF inhibitors in patients with one of these conditions that makes TNF inhibitors contraindicated.

• Precautions: do not use in patients with active infection. Use pneumocystis jiroveci prophylaxis for patients with ANCA-associated vasculitis and lung disease.

• Other diseases that it has been used for: SLE, antiphospholipid antibody syndrome (APS), extraglandular Sjögren's syndrome, IgG4 disease, neuromyelitis optica spectrum disorder, idiopathic thrombocytopenic purpura, autoimmune hemolytic anemia, pemphigus vulgaris, Castleman's disease.

Does not work in spondyloarthropathies.



In some cases plasma infusion or exchange therapy fails to provide a long-term benefit. When autoantibodies are responsible for depletion of ADAMTS13, this is likely a result of the persistance of autoantibody producing B lymphocytes that continue to secrete autoantibodies. Rituximab is an CD20-binding monoclonal antibody that selectively binds to B lymphocytes and mediates their destruction. In HIV-infected people, Rituximab has been used succesfully without evidence of clinical worsening or increased opportunistic infection.

immunopaedia.org

BIOLOGIC AGENTS - B cell targeted therapies- (31)
==========
1-Rituximab (Rituxan) (4):
==========
When can/should rituximab be repeated?
Can other immunosuppressive medications be used with it?

Among RA patients, the response is variable.

Patients who are seropositive (rheumatoid factor and/or anticyclic
citrullinated peptide) are more likely to respond.

All patients deplete their B cells so this does not need to be checked. B cell repopulation occurs at a mean of 8 months post-therapy. Patients who respond tend to by 4 to 6 months. The duration of response varies (median 30 weeks) and patients tend to relapse with reappearance of memory B cells (IgD+CD27) and not naïve B cells.

Retreatment is done when clinical symptoms recur and are not based on B cell counts; however, retreatment is not done sooner than 4 months after previous therapy.

Recently, some physicians are giving one infusion of 1000 mg of rituximab every 6 months to maintain remission in responders to prevent relapse.

Primary nonresponders usually do not respond to additional rituximab courses. These patients can be started on another biologic agent at 6 months after the initial course of two rituximab infusions even if B cells are still depleted without a significant increase in infection risk.

Among ANCA-associated vasculitis patients, rituximab appears to be equivalent to cyclophosphamide.

Patients can be treated with an RA dose schedule or lymphoma (4 weekly doses) schedule. All patients deplete their B cells. Patients relapse with recurrence of B cells at an average of 12 months. Patients can relapse before the reappearance of ANCA.

Some physicians advocate giving 500 mg every 6 months to maintain remission and avoid relapse.

In patients that relapse, a second course of rituximab is as effective as the first course.

Rituximab is reportedly effective in GPA and MPA in patients who are ANCA negative.

BIOLOGIC AGENTS - B cell targeted therapies- (32)
==========
2-Belimumab (Benlysta):
==========
Belimumab (Benlysta) is a fully human IgG1λ monoclonal antibody directed against B lymphocyte stimulator protein (BLyS)/B cell activating factor (BAFF).

BLyS is the same as BAFF and promotes B cell survival,growth, and maturation by binding to three different B cell receptors.

Inhibition of BLyS causes peripheral B cell counts to decrease by 40% to 50%.

Ig levels usually not affected.

Half-life is 11 to 14 days.

What are the indications, efficacy, and toxicities of belimumab (Benlysta)?
==========

• FDA-approved indication: SLE. Does not work in RA.

• Available formulation:
single use vial containing 120 mg or 400 mg of lyophilized powder for reconstitution.

• Dosage:
loading dose of 10 mg/kg IV at 0, 2, and 4 weeks; maintenance 10 mg/kg IV every 4 weeks.
Does not need premedication.
Infusion takes 1 hour.

• Follow-up:
routine monitoring for SLE.

• Efficacy:
SLE patients who were not responding to standard therapy achieved primary endpoint in 43% to 58% of cases.

Patients with severe renal and central nervous system disease were excluded from trials, thus these patients should not be primarily treated with belimumab.

It seems to be most effective in patients with active serologies (low C3/C4, elevated anti-dsDNA antibody) and high BLyS levels (not available for testing).

Manifestations that respond best are fatigue, rash, and arthritis.

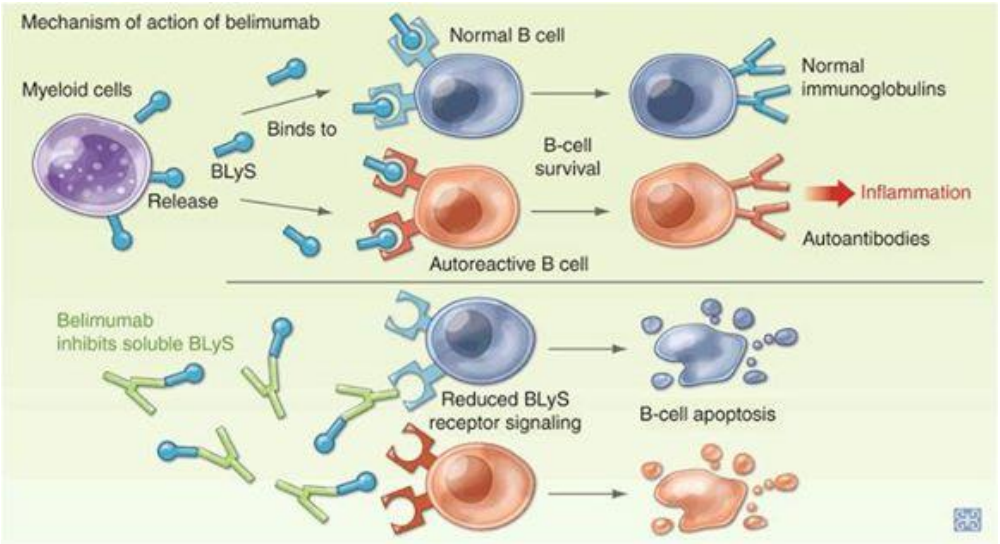
Hematologic abnormalities do not respond well.

• Adverse reactions:
infections, infusion reactions, serious infections, and malignancies were not increased over placebo rate.

• Depression and suicide mildly increased over placebo rate.

• Immunizations: response to killed/inactivated vaccines may be decreased.

• Precautions: do not use in patients with active infection.
Can be given with background immunosuppressive therapy



BIOLOGIC AGENTS - T cell targeted therapies- (33)
==========

Abatacept (Orencia):

-A fully human fusion protein comprising the extracellular portion of CTLA4 and the Fc fragment of IgG1 (CTLA4Ig).

-Abatacept binds to CD80/CD86 on antigen-presenting cells (APCs)
preventing these molecules from binding to their ligand, CD28, on T cells. This interferes with optimal T cell activation resulting in decreased production of proinflammatory cytokines.

-Notably, T cell activation is not completely inhibited because other interactions between APCs and T cells (ICAM-1:LFA-1; CD40:CD40L;LFA-3:CD-2) are not inhibited.

• FDA-approved indication:

RA and polyarticular JIA (>age 6 years, usually after TNF inhibitor) who are inadequate responders to DMARDs (MTX). Can use with DMARDs (MTX).

• Available formulation:
---

single use vial containing 250 mg of lyophilized powder for reconstitution for IV infusion; 125 mg/mL solution in a single dose prefilled glass syringe for SC administration.

• Dosage.

Intravenous dose is weight based
(adults: 500 mg if <60 kg; 750 mg if 60 to 100 kg; 100 mg if >100 kg)
(pediatrics: 10 mg/kg if <75 kg; same as adult dose if >75 kg).
Loading dose at 0, 2, and 4 weeks, then every 4 weeks.
Does not need premedication.
Infusion takes 30 minutes.

• SC dose:
one infusion of weight-based IV dose as above followed by 125

mg SC weekly.
Some physicians do not give IV dose.

• Follow-up:

---

routine monitoring for RA and DMARDs.

• Adverse reactions:

• Infusion reactions: rare. Routine premedication not necessary.

• Infections: routine similar to placebo. Serious infections (3%). Pneumonias increased in patients with chronic obstructive pulmonary disease.
Opportunistic infections rare (0.01 to 0.05 events/100 patient years).

Abatacept may be the safest biologic to use in patients at risk for TB. هاااااااااااااااااااام

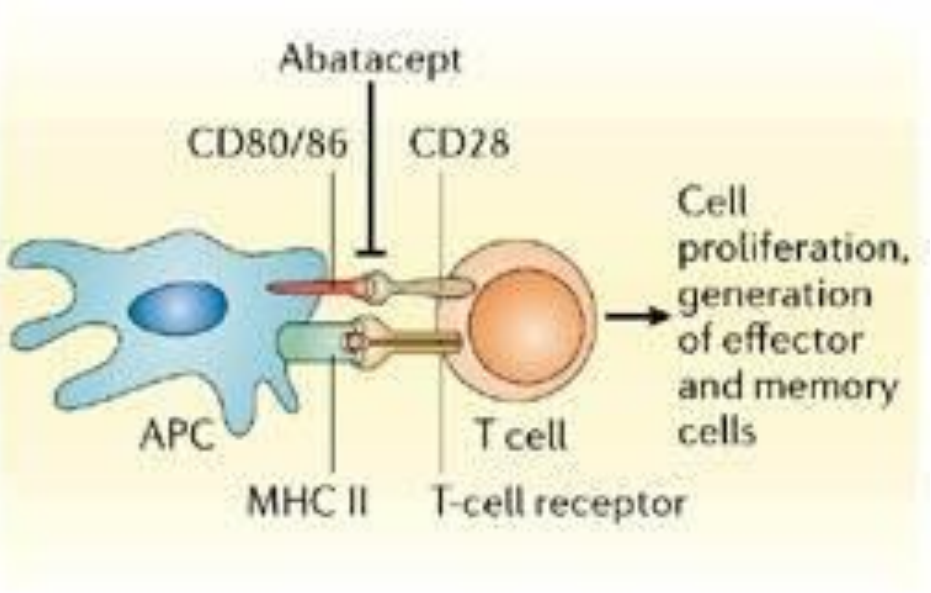
• Malignancy: standardized incidence rates for lung cancer, lymphoma, and other malignancies not increased over background rates of patients with RA who are not on biologics.

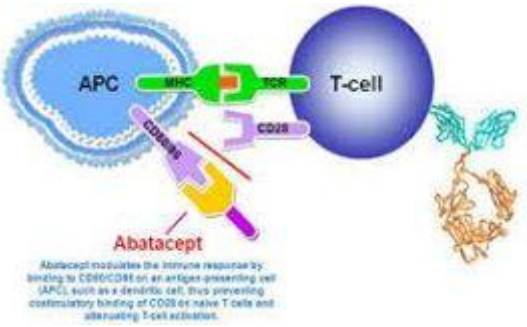
• Immunizations: response to killed/inactivated vaccines may be decreased.

• Others: headache. No increased rate of demyelinating disease, autoimmune phenomenon, CHF, hematologic abnormalities.

• Precautions: do not use in patients with active infection.

• Other diseases: used in PsA and SLE but unclear what subsets it works best for. Being tested in giant cell arteritis (GCA) and Takayasu’s arteritis.





BIOLOGIC AGENTS - (34)
==========

Q-Can live vaccines be given to patients on biologics?

No. Patients should be given a live vaccine at least 4 weeks before starting a biologic therapy. If already on a biologic agent, the patients should stop the biologic at least 3 months before receiving the live vaccine.

Others recommend that a live vaccine can be given if a patient has stopped the biologic for at least 3 to 5 times its half-life (2 to 30 days after tofacitinib; 9 to 15 days after etanercept; 4 to 6 weeks after infliximab and adalimumab;6 to 10 weeks after golimumab, certilizumab, tocilizumab, or abatacept; 9 to 15 weeks after rituximab).

BIOLOGIC AGENTS - Biological drugs & pregnancy (35)
==========

Can biologic agents be given during pregnancy and breastfeeding?

TNF inhibitors and ustekinumab are FDA Pregnancy Classification B medications. They can be used if clinically necessary for the mother's health.

It should be noted that only 4% of the maternal blood level of etanercept is detected in the fetal circulation. Immunoglobulins do not cross placenta before 16 weeks of gestation,thus TNF inhibitors that are monoclonal antibodies should not cross the placenta until then.

Recent data suggest that certilizumab pegol crosses the placenta less than other monoclonal antibodies because it does not have a functional Fc fragment attributable to the pegylation. Animal and observational data support that the congenital malformation rate is not more than the 3% risk in the general population.

One report suggested that the VACTERL anomaly may be associated with TNF inhibitor use but this has not been confirmed.
Importantly, infants born to mothers who have received monoclonal antibodies (especially infliximab) throughout pregnancy should not receive live vaccines until at least 6 months of age as a result of infliximab crossing the placenta and remaining in the infant's circulation for a prolonged period.

Finally, only 4% of etanercept gets into breast milk, whereas very little of the monoclonal TNF inhibitors get into breast milk because
IgG antibodies are not transferred from the maternal circulation to breast milk in high amounts.

All other biologic agents are FDA Pregnancy Classification C medications. They have not been studied sufficiently and therefore are not recommended to be used during pregnancy and probably not during breastfeeding.

Rituximab has been reported to cause transient B cell depletion in the fetus and infant when given to the mother during pregnancy.

VATER (VACTERL) Association

- **V:** vertebral anomalies
- **A:** anal atresia
- **C:** cardiac (including ventricular septal defects)
- **TE:** tracheo-esophageal fistula
- **R:** renal anomalies
- **L:** limb anomalies (thumb or radial hypoplasia, preaxial polydactyly, syndactyly)

Fig. 1 : Roentgenogram of chest posteroanterior view showing scoliosis of thoracic vertebra with convexity to the right.

BIOLOGIC AGENTS - Other biologic agents- (37)
==========
What other biologic agents are being tested in trials which may help treat inflammatory rheumatic diseases? ادوية تحت الاختبار

Cytokine-targeted therapies

• Anti-IL-6 receptor: sarilumab; anti-IL-6: sirukumab, olokizumab.

• Anti-IL-17A receptor: brodalumab; anti-IL-17A: secukinumab, ixekizumab.

• Anti-IL-20: Nnc0109-0012.

• IFN-α inhibitors: anti-IFN-α (sifalimumab); IFN-α kinoid.

• Oral tyrosine kinase inhibitors: fostamatinib (SYK inhibitor), baricitinib (JAK inhibitor).

B cell targeted therapies

• Anti-CD20: ofatumumab; ocrelizumab.

• Anti-CD22: epratuzumab.

• B cell stimulating factor inhibitors: atacicept (BLyS/BAFF, APRIL); tabalumab (anti-BAFF); blisibimod
(fusion protein anti-BAFF).

Other molecules

• Mavrilimumab (antigranulocyte macrophage colony stimulating factor [anti-GM-CSF] receptor α).

• Chemokine inhibitor: CCX354-L2 (CCR1 inhibitor).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BIOLOGIC AGENTS - Eculizumab- (37)
==========

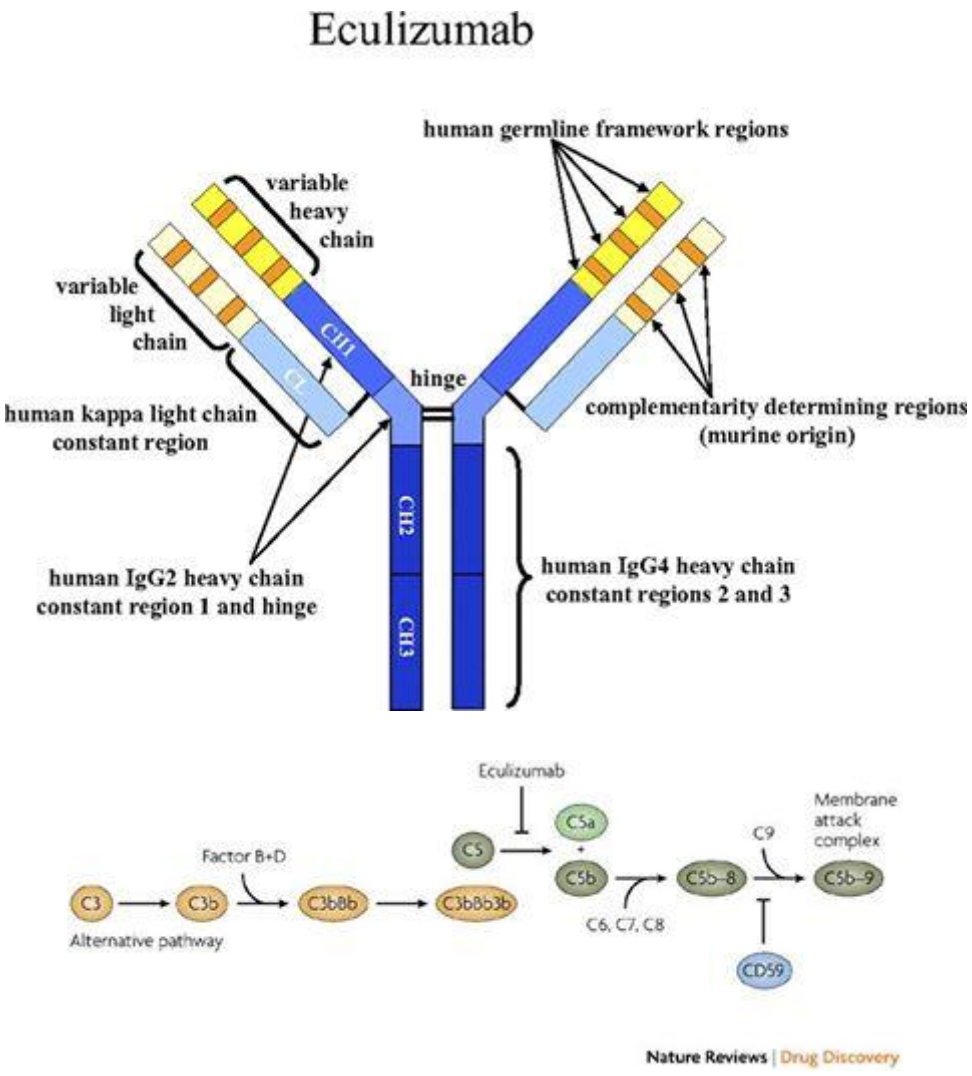
What is eculizumab?

Eculizumab (Soliris) is a humanized IgG2/4κ monoclonal antibody that binds C5 to inhibit its cleavage to C5a and C5b preventing the generation of the terminal complement complex, C5b-9.

It is approved for use to treat the complement-mediated thrombotic microangiopathy occurring in patients with atypical hemolytic
uremic syndrome and to prevent the hemolysis that occurs in patients with paroxysmal nocturnal hemoglobinuria.

Its most feared side effect is meningococcemia.

It costs $450,000 to $600,000 annually for therapy.




SOLIRIS
(eculizumab)
the first medication specifically indicated to treat all patients with PNH
Soliris
(eculizumab)
300 mg/30 mL
(10 mg/mL)
Infusion Only